

UNCLASSIFIED

AD NUMBER
ADB211649
NEW LIMITATION CHANGE
TO Approved for public release, distribution unlimited
FROM Distribution authorized to U.S. Gov't. agencies only; Proprietary Info.; Jan 96. Other requests shall be referred to Commander, Army Medical Research and Materiel Command, Attn: MCMR-RMI-S, Fort Detrick, Frederick, MD 21702-5012.
AUTHORITY
USAMRMC ltr., 21 Apr 97

THIS PAGE IS UNCLASSIFIED

AD _____

CONTRACT NUMBER: DAMD17-92-C-2081

TITLE: Synthesis of Antidotes and Prophylactics for
Organophosphorus Acetylcholinesterase Inhibitors

PRINCIPAL INVESTIGATOR: Richard J. Sundberg, Ph.D.

CONTRACTING ORGANIZATION: University of Virginia
Charlottesville, VA 22901

REPORT DATE: January 1996

TYPE OF REPORT: Final

19960628 037

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Distribution authorized to U.S.
Government agencies only (proprietary information, Jan 96).
Other requests for this document shall be referred to Commander,
U.S. Army Medical Research and Materiel Command, ATTN:
MCMR-RMI-S, Fort Detrick, Frederick, Maryland 21702-5012.

The views, opinions and/or findings contained in this report are
those of the author(s) and should not be construed as an official
Department of the Army position, policy or decision unless so
designated by other documentation.

DTIC QUALITY INSPECTED 1

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE January 1996		3. REPORT TYPE AND DATES COVERED Final (1 Jun 92 - 31 Dec 95)
4. TITLE AND SUBTITLE Synthesis of Antidotes and Prophylactics for Organophosphorus Acetylcholinesterase Inhibitors			5. FUNDING NUMBERS DAMD17-92-C-2081	
6. AUTHOR(S) Richard J. Sundberg, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Virginia Charlottesville, Virginia 22901			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Commander U.S. Army Medical Research and Materiel Command Fort Detrick Frederick, Maryland 21702-5012			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION/AVAILABILITY STATEMENT Distribution authorized to U.S. Government agencies only (proprietary information, Jan 96). Other requests for this document shall be referred to Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RMI-S, Fort Detrick, Frederick, Maryland 21702-5012.			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) New compounds were prepared for evaluation as antidotal and/or prophylactic activity against toxic organophorus acetylcholinesterase inhibitors. One series of compounds consists of the 5-, 6-, 7-, and 8-(N,N-dimethylcarbamoyloxy) derivatives of 1-methylimidazo[1,2-a]pyridinium ion with varying C2 substituents. Fifteen new compounds were prepared. These compounds show substantial activity as inhibitors of acetylcholinesterase (electric eel) but no data are available on <i>in vivo</i> protective activity. A second series of compounds included thirteen new ω -carbamoyloxyalkylimidazolium salts. Some of these compounds show marginal activity as acetylcholinesterase inhibitors. The two lead compounds in this series had shown <i>in vivo</i> activity, but no <i>in vivo</i> data has been obtained for the new compounds. Five additional compounds including two phenols and three enol carbamates were prepared. The report includes synthetic methods, spectroscopic data and elemental analysis for all new compounds prepared.				
14. SUBJECT TERMS Acetylcholinesterase inhibition, prophylactic activity, anti-dotal activity, imidazoles, imidazo[1,2-a]pyridines, carbamates			15. NUMBER OF PAGES 59	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Limited	

GENERAL INSTRUCTIONS FOR COMPLETING SF 298

The Report Documentation Page (RDP) is used in announcing and cataloging reports. It is important that this information be consistent with the rest of the report, particularly the cover and title page. Instructions for filling in each block of the form follow. It is important to **stay within the lines** to meet **optical scanning requirements**.

Block 1. Agency Use Only (Leave blank).

Block 2. Report Date. Full publication date including day, month, and year, if available (e.g. 1 Jan 88). Must cite at least the year.

Block 3. Type of Report and Dates Covered. State whether report is interim, final, etc. If applicable, enter inclusive report dates (e.g. 10 Jun 87 - 30 Jun 88).

Block 4. Title and Subtitle. A title is taken from the part of the report that provides the most meaningful and complete information. When a report is prepared in more than one volume, repeat the primary title, add volume number, and include subtitle for the specific volume. On classified documents enter the title classification in parentheses.

Block 5. Funding Numbers. To include contract and grant numbers; may include program element number(s), project number(s), task number(s), and work unit number(s). Use the following labels:

C - Contract	PR - Project
G - Grant	TA - Task
PE - Program Element	WU - Work Unit Accession No.

Block 6. Author(s). Name(s) of person(s) responsible for writing the report, performing the research, or credited with the content of the report. If editor or compiler, this should follow the name(s).

Block 7. Performing Organization Name(s) and Address(es). Self-explanatory.

Block 8. Performing Organization Report Number. Enter the unique alphanumeric report number(s) assigned by the organization performing the report.

Block 9. Sponsoring/Monitoring Agency Name(s) and Address(es). Self-explanatory.

Block 10. Sponsoring/Monitoring Agency Report Number. (If known)

Block 11. Supplementary Notes. Enter information not included elsewhere such as: Prepared in cooperation with...; Trans. of...; To be published in.... When a report is revised, include a statement whether the new report supersedes or supplements the older report.

Block 12a. Distribution/Availability Statement. Denotes public availability or limitations. Cite any availability to the public. Enter additional limitations or special markings in all capitals (e.g. NOFORN, REL, ITAR).

DOD - See DoDD 5230.24, "Distribution Statements on Technical Documents."

DOE - See authorities.

NASA - See Handbook NHB 2200.2.

NTIS - Leave blank.

Block 12b. Distribution Code.

DOD - Leave blank.

DOE - Enter DOE distribution categories from the Standard Distribution for Unclassified Scientific and Technical Reports.

NASA - Leave blank.

NTIS - Leave blank.

Block 13. Abstract. Include a brief (*Maximum 200 words*) factual summary of the most significant information contained in the report.

Block 14. Subject Terms. Keywords or phrases identifying major subjects in the report.

Block 15. Number of Pages. Enter the total number of pages.

Block 16. Price Code. Enter appropriate price code (*NTIS only*).

Blocks 17. - 19. Security Classifications. Self-explanatory. Enter U.S. Security Classification in accordance with U.S. Security Regulations (i.e., UNCLASSIFIED). If form contains classified information, stamp classification on the top and bottom of the page.

Block 20. Limitation of Abstract. This block must be completed to assign a limitation to the abstract. Enter either UL (unlimited) or SAR (same as report). An entry in this block is necessary if the abstract is to be limited. If blank, the abstract is assumed to be unlimited.

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the US Army.

na Where copyrighted material is quoted, permission has been obtained to use such material.

na Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

✓ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

na In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

na For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

na In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

na In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

na In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.


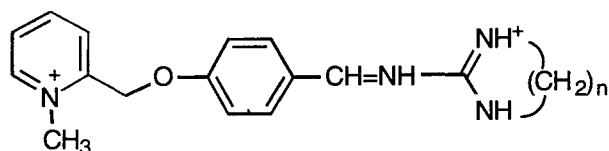
 Jan 24, 1996
PI - Signature Date

Table of Contents

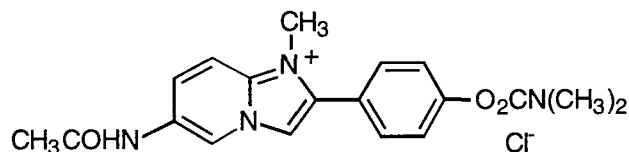
Introduction.....	1
Table 1. New Compounds Submitted.....	4
Synthetic Methods.....	8
A. Carbamoyloxyalkylimidazolium Salts	8
B. Carbamoyloxyimidazo[1,2-a]pyridinium Salts	10
C. Carbamoyl Enolates of Choline Analogs	13
D. Miscellaneous Compounds	14
Biological Results.....	14
Experimental Section	18
References.....	54

Introduction

The purpose of this work was to prepare a number of quaternary heteroaromatic salts for evaluation as antidotal and/or prophylactic activity against organophosphorus inhibitors of acetylcholinesterase. The initial impetus for work in this particular type of compounds came from recognition of both antidotal and prophylactic activity in several compounds prepared in an earlier antiparasitic program. Specifically, compounds BL08205 and BL09042 showed antidotal activity and BL55142 showed prophylactic activity.



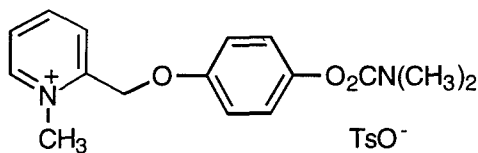
n=2	BL08205	70-90% survival of 2 LD ₅₀ GD
n=3	BL09042	70% survival of 2LD ₅₀ GD



BL55142	100% survival of 2LD ₅₀ GD at 15 min pretreatment
---------	--

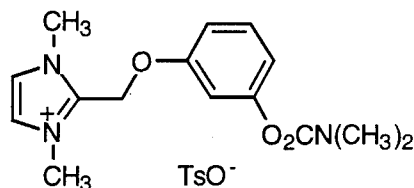
During the period January 1, 1989 - June 30, 1991 these leads were pursued under the auspices of contract DAMD-17-89-C-9014. A total of 75 new compounds were prepared. These included various substituted 2-aryloxymethylpyridinium and imidazolium salts. These compounds indicated relatively little activity. Also prepared were a number of 2-[2-, 3-, and 4-carbamoyloxyphenyl]imidazo[1,2-a]pyridinium salts and 2-(carbamoyloxyphenoxymethyl) derivatives of imidazole, pyridine, quinoline, benzimidazole and imidazo[1,2-a]pyridine. Many of these compounds were active. Results were published in two papers in 1993 (1). A number of these compounds show inhibition of acetylcholinesterase (electric eel) with compound

BM01738 being most active ($IC_{50} = 10$ nM). Although this compound was not particularly promising *in vivo*, the pyridinium salt BM01265 showed substantial prophylactic activity.



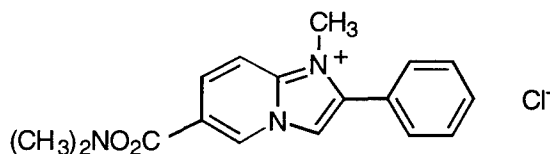
BM01265

80-100% Survival of 2 LD₅₀ GD at
60 min. pretreatment 0.9-62.5 mg/kg



BM01738

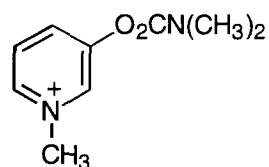
In the course of that work a single example having a carbamoyloxy substituent on the heterocyclic ring was prepared. This compound BM08648 showed some prophylactic activity and a principle emphasis of the current work was to systematically vary the position of substitution and the nature of the 2-substituent for the imidazo[1,2-a]pyridine series.



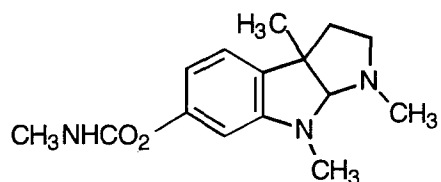
BM08648

80% Survival of 2 LD₅₀ GD of 60 min. pretreatment at 35.6 mg/kg

The prophylactic activity of several heterocyclic carbamates is well known with pyridostigmine and physostigmine having been well-studied. The positive charge on such compounds presumably makes them particularly good substrates for acetylcholinesterase (2, 3).

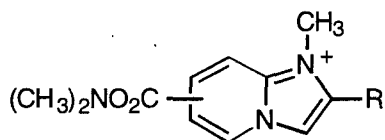


pyridostigmine



physostigmine

We successfully prepared a series of 16 compounds (including the previously prepared BM08648) representing the 2-H, 2-methyl, 2-isopropyl, and 2-phenyl compounds with N, N-dimethylcarbamoyloxy substituents at each of the other ring positions.



R = H, CH₃, (CH₃)₂CH-, C₆H₅

In addition, thirteen carbamoyloxyalkylimidazolium salts which were part of the series begun under the auspices of DAMD-17-89-C-9014 were prepared. We also prepared a few enol carbamates from aminoketones having structure similarity to acetylcholine or acetylcholine mimics. In all 33 new compounds were prepared. They are listed in Table I in chronological order of submission.

Table 1. New Compounds Submitted

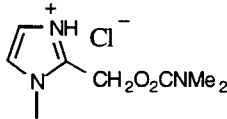
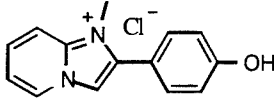
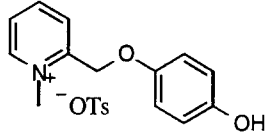
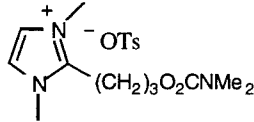
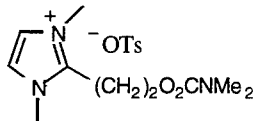
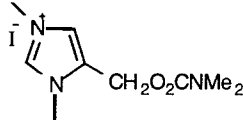
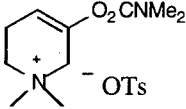
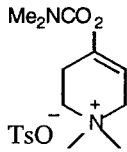
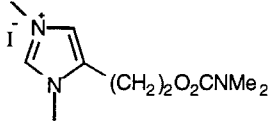
Our sample Number	WRAIR Bottle Number	WR Number	Date of Submission	Structure
KC005	BM14299	279314AA	Aug 31 92	
KC012	BM14306	279315AA	Aug 31 92	
KC020	BM14324	279317AA	Aug 31 92	
KC017	BM14315	279316AA	Aug 31 92	
PN38	BM16177	279316AB	Feb 11 93	
PN68	BM16186	279439AA	Feb 11 93	
PN-177	BM17816	279530AA	June 14 93	
PN-226	BM17825	279531AA	June 14 93	
PN-236	BM17834	279532AA	June 14 93	
PN-294	BM17843	279533AA	June 14 93	

Table 1. New Compounds Submitted (continued)

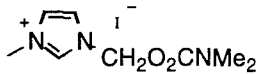
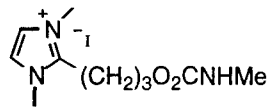
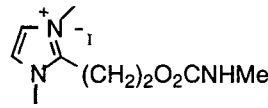
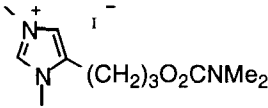
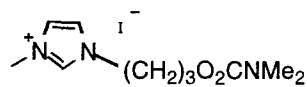
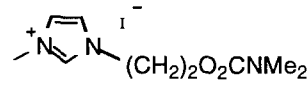
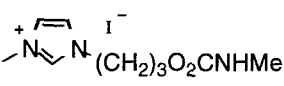
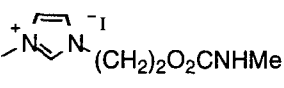
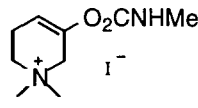
Our sample Number	WRAIR Bottle Number	WR Number	Date of Submission	Structure
PN-II-32	BM 18957	279570	Aug 17 93	
PN-II-62	BM 18966	279571	Aug 17 93	
PN-II-68	BM 18975	279572	Aug 17 93	
PN-I-292	BM 19070	279580	Sept 15 93	
PN-II-108	BM 19089	279581	Sept 15 93	
PN-II-112	BM 19098	279582	Sept 15 93	
PN-II-178	BN 34803	279652	Dec 13 93	
PN-II-184	BN 34812	279653	Dec 13 93	
PN-II-198	BN 34821	279654	Dec 13 93	

Table 1. New Compounds Submitted (continued)

Our sample Number	WRAIR Bottle Number	WR Number	Date of Submission	Structure
PN-II-222	BN 34830	279655	Dec 13 93	
PN-II-278	BN 36049	279700	March 15 94	
PN-III-28	BN 36058	279701	March 15 94	
PN-II-258	BN 36030	279699	March 15 94	
PN-III-190	BN38856	279837	June 15 94	
PN-III-220	BN38865	279838	July 8 94	
PN-III-236	BN38874	279839	July 8 94	
PN-III-240	BN38883	279848	July 8 94	

Table 1. New Compounds Submitted(continued)

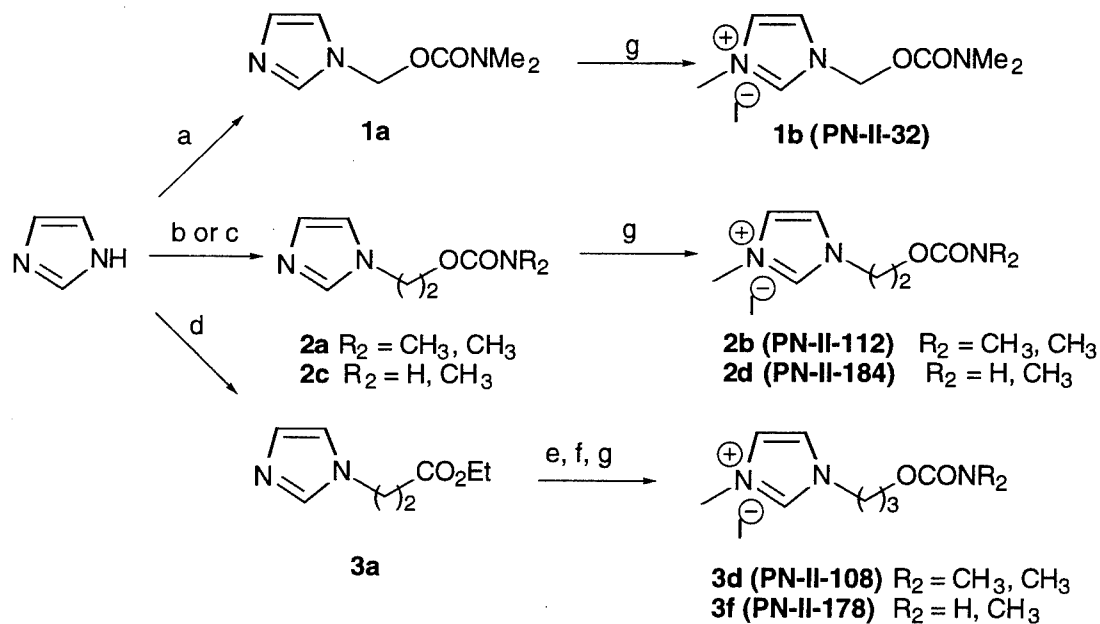
Our sample Number	WRAIR Bottle Number	WR Number	Date of Submission	Structure
PN-III-268	BN40481	279951	Sept 15 94	
PN-IV-33	BN40507	279953	Sept 15 94	
PN-IV-36	BN40490	279952	Sept 15 94	
SJ-II-43	BN63788	280471	Oct 16 95	
SJ-II-39	BN63799	280470	Oct 16 95	
SJ-II-100	BN64810	280495	Dec 4 95	
SJ-II-95	BN64801	280494	Dec 4 95	

Synthetic Methods

A. Carbamoyloxyalkylimidazolium Salts

1-Substituted carbamoyloxyimidazolium salts were prepared by N-alkylation of the imidazole using BuLi, $\text{CH}_2=\text{O}$ ($n=1$), BuLi, oxirane ($n=2$), and NaH, $\text{CH}_2=\text{CHCO}_2\text{C}_2\text{H}_5$ then LiAlH_4 , respectively. The 1-(ω -hydroxyalkyl)imidazoles were then carbamoylated and quaternized. The methods are summarized in Scheme I and details are given in the Experimental Section.

Scheme I

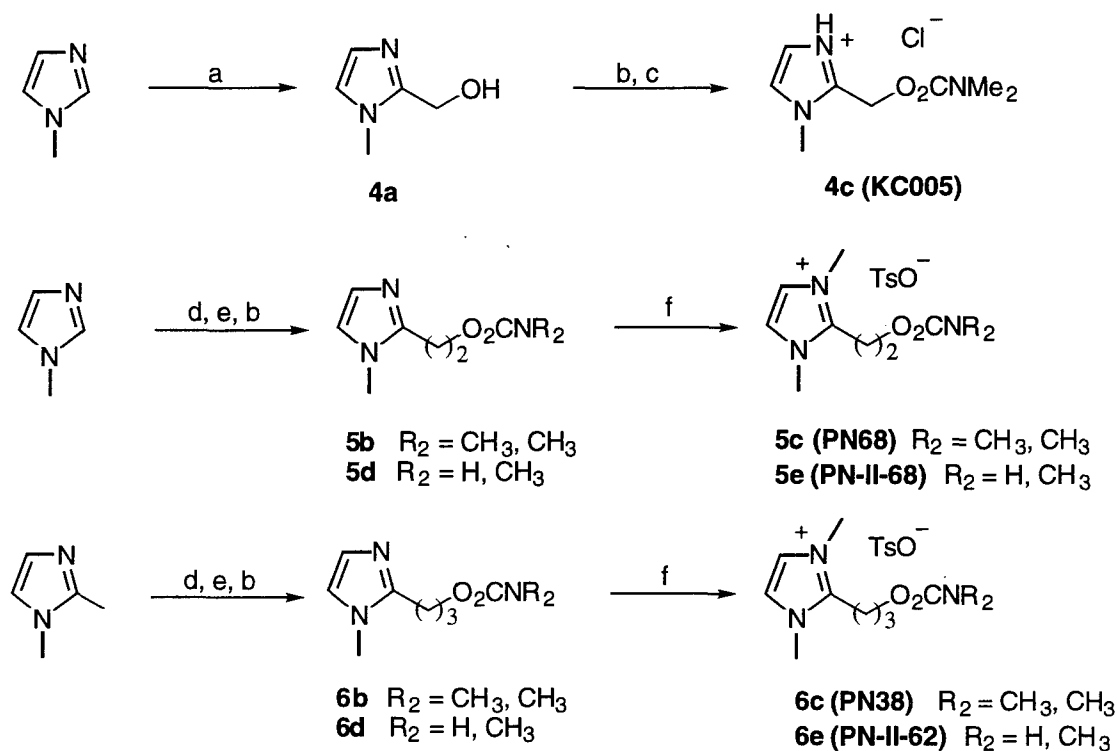


a) BuLi; $(\text{CH}_2\text{O})_n$; Me_2NCOCl . b) BuLi; ethylene oxide; Me_2NCOCl .

c) $\text{CH}_3\text{N}=\text{C}=\text{O}$; d) Ethyl acrylate, cat. NaH. e) LiAlH_4 . f) NaH; Me_2NCOCl ; g) MeI.

Scheme II depicts the synthesis of 2-(N,N-dimethylcarbamoyloxymethyl), 2-[2-(N,N-dimethylcarbamoyloxy)ethyl] and 2-[3-(N,N-dimethylcarbamoyloxy)propyl] imidazolium salts. Chain introduction or extension was accomplished by alkylation of lithium intermediates with formaldehyde or oxirane. The hydroxyl group was then carbamoylated and the heterocyclic molecule was quaternized. Details are given in the Experimental Section.

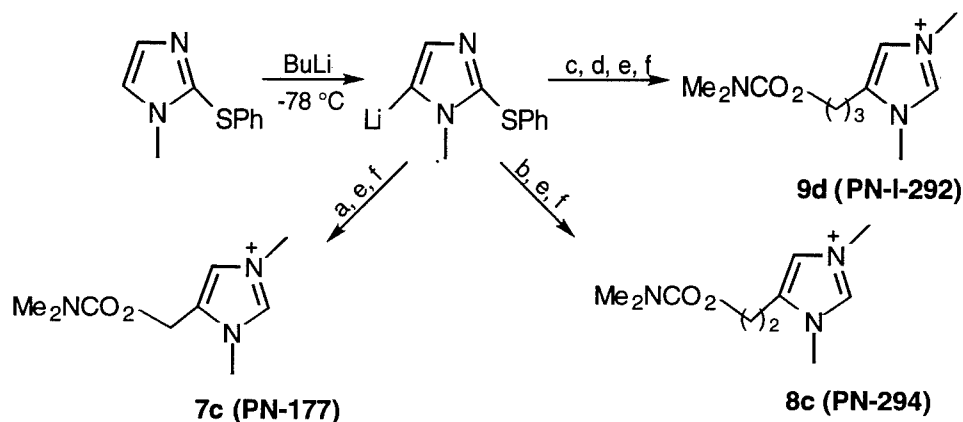
Scheme II



a) CH_2O . b) Me_2NCOCl . c) HCl . d) BuLi . e) Oxirane. f) MeOsT .

Alkyl groups were introduced at the 4-position of the imidazole ring using a phenylthio substituent to block the 2-position. (4) Hydroxymethyl, 2-hydroxyethyl and 3-hydroxypropyl groups were then introduced using formaldehyde, oxirane and oxetane/BF₃, respectively. The alcohols were then carbamoylated. Desulfurization was accomplished with Raney nickel prior to Quaternization. These methods are outlined in Scheme III and described in Experimental Section.

Scheme III



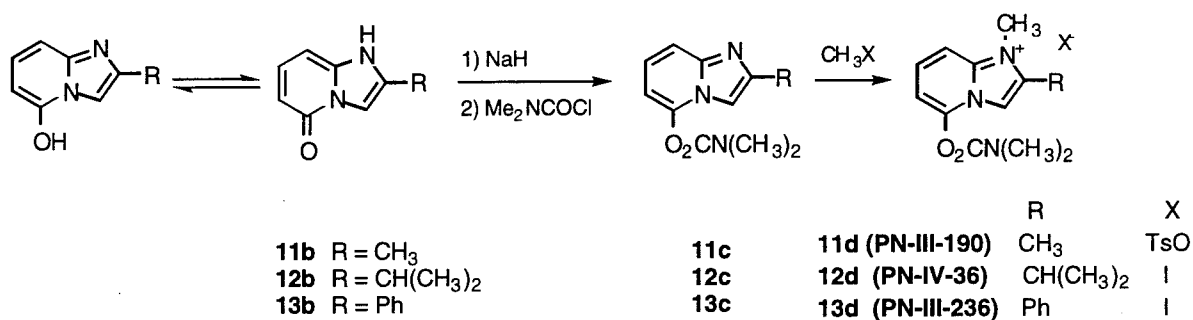
a) (CH₂O)_n; Me₂NCOCl. b) Oxirane; Me₂NCOCl. c) Oxetane, BF₃-Et₂O.
d) NaH, DMF; Me₂NCOCl. e) Raney Ni desulfurization. f) MeI.

B. Carbamoyloxyimidazo[1,2-a]pyridinium Salts

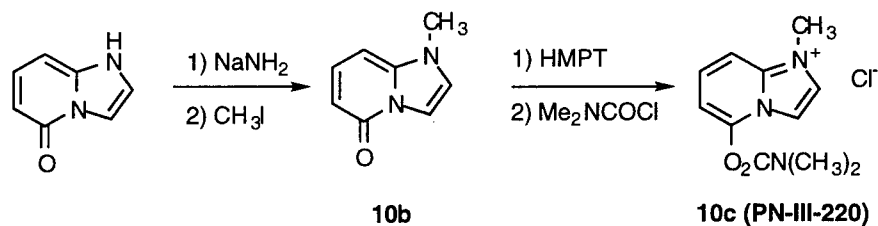
5-Hydroxyimidazo[1,2-a]pyridine was prepared from 5-aminoimidazo[1,2-a]pyridine by reacting with 70% aqueous H₂SO₄. (5) This reaction was also applicable to the 2-methyl and 2-phenyl derivatives. The 2-(2-propyl) derivative was prepared from 2-amino-6-hydroxypyridine (5) and 1-bromo-3-methylbutan-2-one. (6) The 5-hydroxyimidazo[1,2-a]pyridines are in tautomeric equilibria with the 5-keto tautomers and are very weakly acidic. For this reason, carbamoylation was carried out on the sodium salts prepared with NaH. Quaternization could then be done with

methyl iodide (Scheme IV). In the case of **10a** the N-methylation was done first (Scheme V).

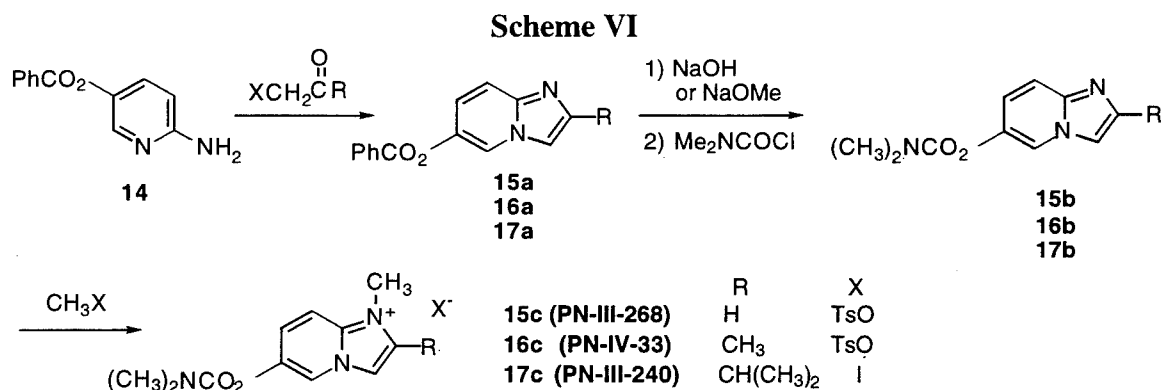
Scheme IV



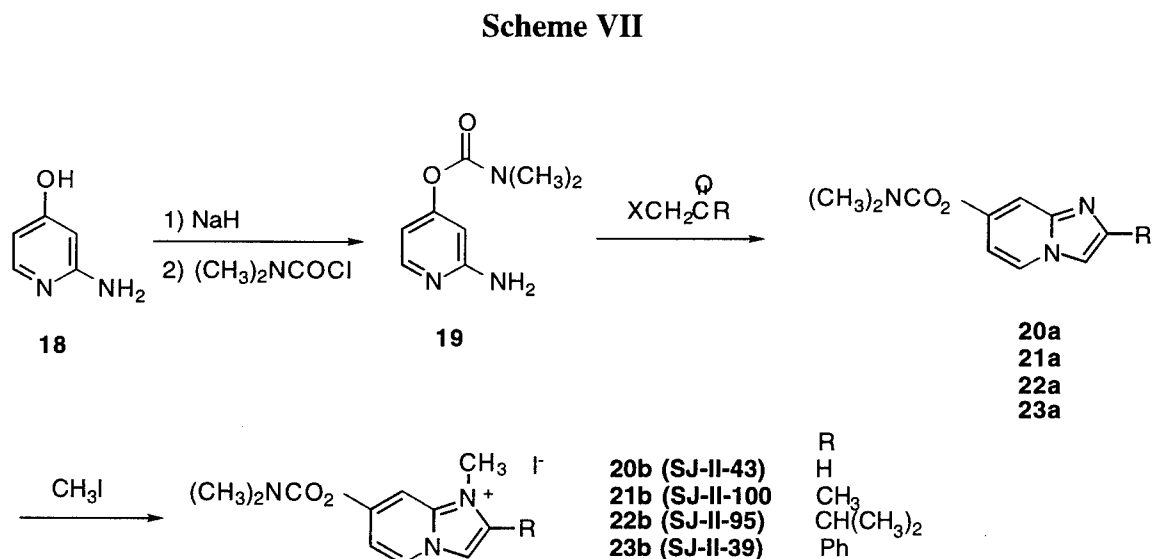
Scheme V



2-Amino-6-benzoyloxypyridine was prepared by an adaptation of the method of Moore and coworkers. (7) Details are given in the Experimental Section. This compound was cyclized with an appropriate α -halocarbonyl compound, solvolyzed, carbamoylated and then quaternized with methyl iodide or methyl tosylate (Scheme VI).

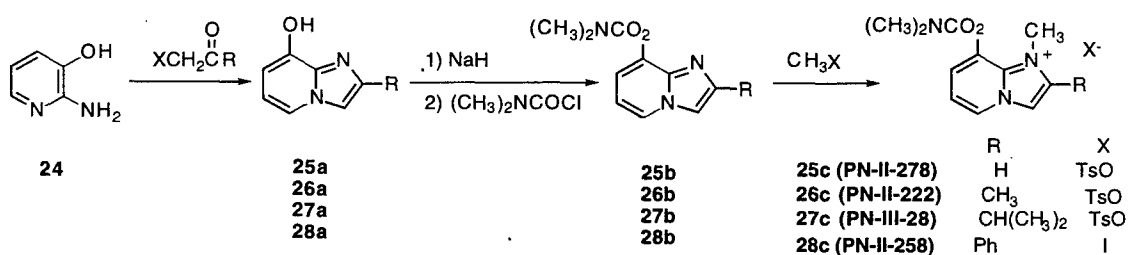


An existing route to 2-amino-4-hydroxypyridine was substantially improved during the course of this work. (8) As with the 5-isomers the possibility of a tautomeric equilibrium exists and carbamoylation was best done with the sodium salt of 2-amino-4-hydroxypyridine. The product, 4-(N,N-dimethylcarbamoyloxy)-2-aminopyridine can rearrange by O-to-N acyl migration but it was possible to cyclize the compound directly with the various α -halomethyl reactants. This provided a more convergent route than was employed for the other series of compounds. Quaternization was then done with methyl iodide (Scheme VII).



The 8-substituted imidazo[1,2-a]pyridine derivatives were prepared beginning with commercially available 2-amino-3-hydroxypyridine. (9) Each of the 8-hydroxy intermediates was carbamoylated and then quaternized with methyl iodide or methyl tosylate (Scheme VIII).

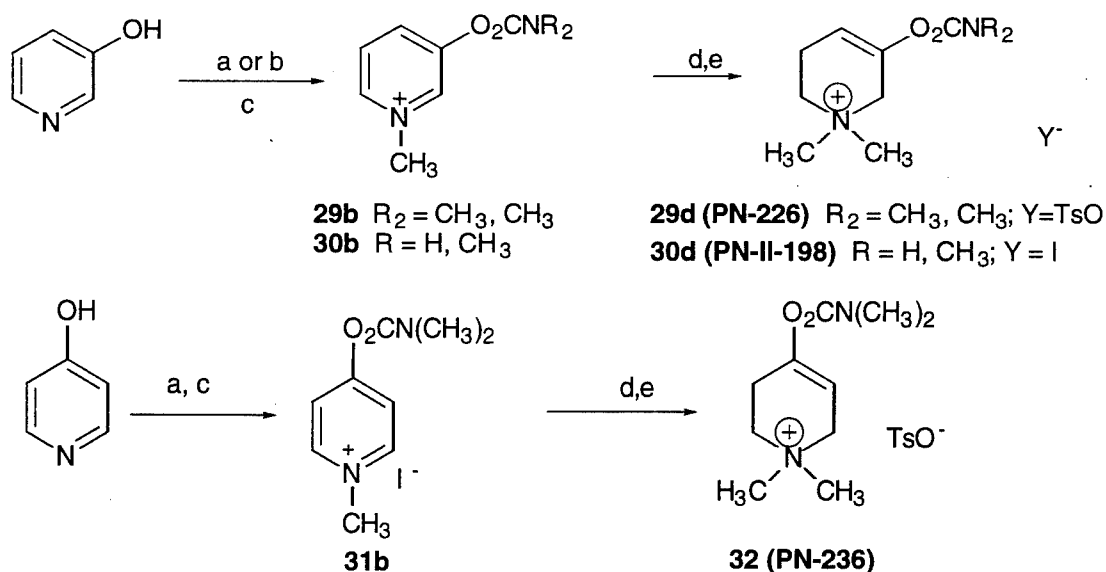
Scheme VIII



C. Carbamoyl enolates of Choline Analogs

The enolates of 1-methyl-3-piperidone and 1-methyl-4-piperidone were prepared from 3-hydroxyl and 4-hydroxypyridine, respectively. The piperidines were first carbamoylated with N,N-dimethylcarbamoyl chloride and then reduced with NaBH₄ to give the enol carbamates (tetrahydroxypyridines). The enol carbamate were then quaternized. Compound BM34821, the N-methylcarbamate of the enol of 1-methyl-3-piperidone was prepared following the same route using methyl isocyanide for carbamoylation. The route is outlined in Scheme IX and details are given in the Experimental Section.

Scheme IX



a) NaH, $\text{ClCON}(\text{CH}_3)_2$; b) $\text{CH}_3\text{N}=\text{C}=\text{O}$; c) CH_3OTs or CH_3I ; d) NaBH_4 ; e) CH_3OTs .

D. Miscellaneous Compounds

Two phenols, KC012/BM14306 and KC020/BM14324 which are precursors of active carbamates were submitted to determine if the uncarbamoyleated compounds show any activity, since Gandour, Quinn and coworkers had demonstrated that the phenol precursor of neostigmine has activity as an AChE inhibitor (10). These compounds had been prepared earlier as intermediates and are described in the final report for project DAMD-17-89-C-9014.

Biological Results

All compounds were submitted to Walter Reed Army Institute of Research for evaluation of prophylactic and antidotal activity against organophosphorus inhibitors of AChE. In order to have preliminary and more rapid evidence of activity to guide synthetic efforts we also conducted *in vitro* assays using electric eel type AChE, following the method of Ellman (11). The available data are given in Tables 2 and 3.

Table 2. Activity of Carbamoyloxy Imidazo[1,2-a]pyridinium Salts as AChE Inhibitors

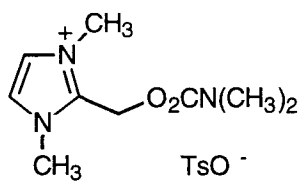
Our Sample	WRBN	IC ₅₀	R	Carbamoyloxy Substitution
PN-III-220	BN38865	0.04±0.01	H	5
PN-III-194	BN38856	0.03±0.01	CH ₃	5
PN-IV-36	BN40490	0.014±0.005	CH(CH ₃) ₂	5
PN-III-236	BN38874	0.09±0.01	Ph	5
PN-III-268	BN40481	15±2.5	H	6
PN-IV-33	BN40507	31±12	CH ₃	6
PN-III-240	BN38883	16±2.0	CH(CH ₃) ₂	6
DD-III-174	BM08648 ^a	50	Ph	6
SJ-II-43	BN63788	1.9±0.5	H	7
SJ-II-100	BN64810	7.4±0.5	CH ₃	7
SJ-II-95	BN64801	7.5±1.2	CH(CH ₃) ₂	7
SJ-II-39	BN63799	11±0.3	Ph	7
PN-II-278	BN36049	0.04±0.005	H	8
PN-II-222	BN34830	0.075±0.005	CH ₃	8
PN-III-28	BN36058	1.8±0.2	CH(CH ₃) ₂	8
PN-II-258	BN36030	2.5±0.3	Ph	8

a) Final report DAMD-17-89-C-9014

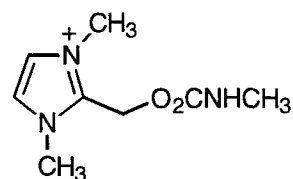
Table 3. Inhibition of Acetylcholinesterase by Carbamoyloxyalkylimidazolium Salts

<u>Compound</u>	<u>Our sample No</u>	<u>WRAIR Bottle No</u>	<u>IC₅₀ (mM)</u>
1b	PN-II-32	BM 18957	>100
2b	PN-II-112	BM 19098	>100
3d	PN-II-108	BM 19089	>100
2d	PN-II-184	BN 34812	>100
3f	PN-II-178	BN 34803	>100
a	DD-II-61	BM 03698	29.1-33.0
5c	PN-68	BM 16186	19.3-21.1
6c	PN-38	BM 16177	25.8-29.9
a	JC-I-72A	BM 02646	12.3-12.9
5e	PN-II-68	BM 18975	12.4-15.0
6e	PN-II-62	BM 18966	65.0-65.6
7c	PN-177	BM 17816	>100
8c	PN-294	BM 17843	72.9-74.0
9d	PN-I-292	BM 19070	39.0-41.7

a. Prepared under contract DAMD-17-89-C-9014. Biological results obtained during current period.



BM03698



BM02646

Table 4. *In Vivo* Data for BM03698 and BM02646

		Per Cent Survival		
	Dose	t - 60 min	t - 15 min	t + 10 min
BM03698	6.25	30	50	40, 50
	25	90	100	100, 70
	100	100	90	80, 20
BM02646	6.25	90	90	70, 50
	25	90	100	90, 80
	100	100	90	80, 60

Experimental Section

A. Carbamoyloxyalkylimidazolium Salts

1-[(N,N-Dimethylcarbamoyloxy)methyl]-1*H*-imidazole (1a) To a cooled solution (-15 °C) of imidazole (6.81 g, 0.1 mol) in dry THF (130 mL) was added dropwise a solution of *n*-BuLi in hexane (44 mL, 0.11 mol). The mixture was stirred at -10 °C for 30 min then predried paraformaldehyde (4.5 g, 0.15 mol) was added in small portions. After being stirred at -5 °C for 10 min the cooled bath was removed and the reaction mixture was stirred at room temperature overnight. N,N-dimethylcarbamoyl chloride (1.38 mL, 0.15 mol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was quenched with dilute aqueous HCl solution then extracted with ether (3 x 50 mL). The aqueous layer was basified with 20% NaOH solution and extracted with CH₂Cl₂ (4 x 70 mL). The organic layers were washed with H₂O (30 mL), brine (30 mL) and dried (Na₂SO₄). Removal of solvent gave a crude product which was purified by column chromatography (silica gel, CHCl₃-MeOH, 9:1) to give **1a** (12.4 g, 73%) as an off-white solid from EtOAc/hexane; mp 72-73 °C; *R*_f = 0.48 (CHCl₃-MeOH, 9:1); ¹H NMR (CDCl₃) δ 7.72 (s, 1 H), 7.14 (s, 1 H), 7.04 (s, 1 H), 5.86 (s, 2 H), 2.91 (s, 3 H), 2.88 (s, 3 H); ¹³C NMR (CDCl₃) δ 154.74, 138.09, 129.57, 119.51, 68.36, 36.36, 35.71. Anal. Calcd for C₇H₁₁N₃O₂: C, 49.69; H, 6.55; N, 24.92. Found: C, 49.72; H, 6.52; N, 24.92.

General Procedure for Quaternization of ω-Carbamoyloxyimidazoles A mixture of carbamate and methyl iodide or methyl *p*-toluenesulfonate (1.5 equiv) in dry THF (or acetonitrile) was maintained at 60 °C overnight. Ether was then added and the reaction mixture was cooled in ice. The precipitate was collected and purified by recrystallization.

3-Methyl-1-[(N,N-dimethylcarbamoyloxy)methyl]-1*H*-imidazolium Iodide (1b) (PN-II-32, BM18957) Following the general procedure for quaternization, the reaction of **1a** (2.3 g, 13.6 mmol) with methyl iodide (1.69 mL, 27 mmol) in dry THF (10 mL) gave a crude white solid **1b** (4.16 g, 98%) which was recrystallized in MeOH/Et₂O: mp 171-172 °C; IR (KBr)_v_{max} 3155, 3102, 1701, 1180, 1147, 1054 cm⁻¹.

¹H NMR (DMSO-d₆) δ 9.32 (s, 1 H), 7.85 (s, 1 H), 7.73 (s, 1 H), 6.05 (s, 2 H), 3.88 (s, 3 H), 2.86 (s, 3 H), 2.83 (s, 3 H); ¹³C NMR (DMSO-d₆) δ 153.86, 137.97, 123.75, 122.44, 36.19, 36.05, 35.60. Anal. Calcd for C₈H₁₄N₃O₂: C, 30.88; H, 4.53; N, 13.50. Found: C, 30.94; H, 4.57; N, 13.50.

1-[2-(N,N-Dimethylcarbamoyloxy)ethyl]-1H-imidazole (2a) To a cooled solution (-40 °C) of imidazole (6.8 g, 0.1 mol) in dry THF (200 mL) was added slowly a solution of *n*-BuLi in hexane (45.8 mL, 0.11 mol). The mixture was stirred for 30 min and cooled ethylene oxide (10 mL, 0.2 mol) was added at once via canula. The reaction mixture was stirred at room temperature overnight and then N,N-dimethylcarbamoyl chloride (13.8 mL, 0.15 mol) was added. After being stirred at room temperature overnight the mixture was quenched with 100 mL of cold water. Organic solvent was removed under aspirator pressure. The aqueous mixture was saturated with NaCl, then extracted with CHCl₃ (5 x 100 mL). The organic layers were washed with brine, dried (Na₂SO₄) and filtered. Removal of solvent to dryness gave a yellow solid. Purification of the crude product by column chromatography (silica gel; CHCl₃-MeOH, 19:1) gave **2a** (14.4 g, 79%) as a white solid from EtOAc/hexane: mp 80-81 °C; R_f = 0.36 (CHCl₃-MeOH, 9:1); ¹H NMR (CDCl₃) δ 7.51 (s, 1 H), 7.07 (s, q H), 6.96 (s, 1 H), 4.33 (t, 2 H, J = 5.2 Hz), 4.21 (t, 2 H, J = 5.2 Hz), 2.91 (s, 3 H), 2.86 (s, 3 H). Anal. Calcd for C₈H₁₃N₃O₂: C, 52.45; H, 7.15; N, 22.94. Found: C, 52.38; H, 7.18; N, 22.83.

3-Methyl-1-[2-(N,N-dimethylcarbamoyloxy)ethyl]-1H-imidazolium Iodide (2b) (PN-II-112, BM19098) Following the general procedure for quaternization, the reaction of **2a** (1.83 g, 10 mmol) with methyl iodide (2.5 mL, 40 mmol) in dry THF (10 mL) yielded **2b** (2.85 g, 87%) as a white solid from acetone/ether: mp 87-88 °C; IR (KBr) ν_{max} 3146, 3084, 1701, 1192 cm⁻¹; ¹H NMR (DMSO-d₆) δ 9.15 (s, 1 H), 7.77 (brs, 1 H), 7.72 (br s, 1 H), 4.45 (t, 2 H, J = 4.8 Hz), 4.29 (t, 2 H, J = 4.8 Hz), 3.86 (s, 3 H), 2.78 (s, 6 H); ¹³C NMR (DMSO-d₆) δ 154.89, 136.86, 123.59, 122.71, 63.03, 48.39, 36.08, 35.89, 35.56. Anal. Calcd for C₉H₁₆N₃O₂: C, 33.24; H, 4.96; N, 12.92. Found: C, 33.32; H, 4.99; N, 12.87.

Ethyl 3-(Imidazol-1-yl)propionate (3a) A mixture of imidazole (6.8 g, 0.1 mol) and NaH (48 mg, 2 mmol) in dry THF (100 mL) was stirred for 15 min at room

temperature. Ethyl acrylate (13 mL, 0.12 mol) was then added at once. After being stirred at 60 °C for 2 days, the reaction mixture was cooled in an ice bath and quenched with water. The organic solvent was removed under aspirator pressure. The aqueous mixture was basified with aqueous 20% NaOH solution to pH=11, saturated with NaCl and then extracted with CH₂Cl₂. The organic layers were washed with brine, dried (Na₂SO₄) and filtered. Removal of the solvent to dryness gave a dark yellow liquid. Purification of the crude product by column chromatography on silica gel (CHCl₃-MeOH, 9:1) gave **3a** (14.7 g, 87%), a very pale yellow liquid: R_f = 0.39 (CHCl₃-MeOH, 9:1); ¹H NMR (CDCl₃) δ 7.51 (s, 1 H), 7.04 (s, 1 H), 6.94 (s, 1 H), 4.27 (t, 2 H, J = 6.6 Hz), 4.14 (q, 2 H, J = 7.2 Hz), 2.77 (t, 2 H, J = 6.6 Hz), 1.24 (t, 3 H, J = 7.2 Hz); ¹³C NMR (CDCl₃) δ 170.34, 137.12, 129.50, 118.68, 60.96, 42.14, 35.87, 13.94.

1-(3-Hydroxypropyl)-1H-imidazole (3b) To an ice-cooled mixture of LiAlH₄ (0.9 g, 23.8 mmol) in THF (30 mL) was added dropwise a solution of **3a** (2 g, 11.88 mmol) in THF (5 mL). After 10 min the ice-bath was removed and the mixture was stirred at room temperature for 2 h. The reaction mixture was then cooled in an ice bath and sequentially quenched with water (0.9 mL), 20% NaOH solution (0.8 mL) and water (2.7 mL). The mixture was filtered with the aid of Celite. The filtered cake was washed thoroughly with hot THF. Evaporation of the solvent to dryness gave **3b** (1.5 g, 100%) as a colorless liquid: R_f = 0.12 (CHCl₃-MeOH, 9:1); ¹H NMR (CDCl₃) δ 7.46 (s, 1 H), 7.04 (s, 1 H), 6.93 (s, 1 H), 4.12 (t, 2 H, J = 6.7 Hz), 3.60 (t, 2 H, J = 5.7 Hz), 1.99 (m, 2 H); ¹³C NMR (CDCl₃) δ 137.39, 129.12, 118.91, 57.99, 43.35, 33.28.

1-[3-(N,N-Dimethylcarbamoyloxy)propyl]-1H-imidazole (3c) A solution of N,N-dimethylcarbamoyl chloride (0.71 mL, 7.72 mmol) in THF (3 mL) was added dropwise to a slurry mixture of **3b** (0.65 g, 5.15 mmol) and NaH (0.17 g, 7.0 mmol) in THF (12 mL) at reflux temperature. The reaction mixture stirred at that temperature for 6 h, and was then cooled to room temperature, quenched with water (15 mL), basified to pH=10, saturated with NaCl and extracted with CHCl₃ (4 x 30 mL). The organic layers were washed with brine (30 mL), dried (Na₂SO₄) and filtered. Removal of the solvent gave a brown liquid. Column chromatography (silica gel,

CHCl₃-MeOH, 9:1) of the crude product gave **3c** (0.71 g, 69%) as a colorless liquid: *R*_f = 0.40 (CHCl₃-MeOH, 9:1); ¹H NMR (CDCl₃) δ 7.48 (s, 1 H), 7.05 (s, 1 H), 6.94 (s, 1 H), 4.03-4.10 (m, 4 H), 2.90 (s, 6 H), 2.07-2.16 (m, 2 H); ¹³C NMR (CDCl₃) δ 155.85, 136.81, 129.24, 118.51, 61.52, 43.50, 36.12, 35.54, 30.38. Anal. Calcd for C₉H₁₅N₃O₂·2/3H₂O: C, 51.66; H, 7.86; N, 20.08. Found: C, 51.35; H, 7.86; N, 19.93.

3-Methyl-1-[3-(N,N-dimethylcarbamoyloxy)propyl]-1*H*-imidazolium Iodide (3d)
(PN-II-108, BM19089)

Following the general procedure for quaternization, the reaction of **3c** (0.513 g, 2.5 mmol) with methyl iodide (0.32 mL, 5.2 mmol) in THF (5 mL) yielded a thick, pale yellow oil which gave a white solid **3d** (0.85 g, 96%) on standing in the freezer. Analytical sample was recrystallized from acetone: mp 117.5-118 °C; IR (KBr) *v*_{max} 3142, 3067, 1703, 1197 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 9.13 (s, 1 H), 7.78 (d, 1 H, *J* = 1.5 Hz), 7.71 (d, 1 H, *J* = 1.5 Hz), 4.24 (t, 2 H, *J* = 7.1 Hz), 4.00 (t, 2 H, *J* = 6.0 Hz), 3.84 (s, 3 H), 2.79 (s, 6 H), 2.07-2.16 (m, 2 H). Anal. Calcd for C₁₀H₁₈N₃O₂: C, 35.39; H, 5.35; N, 12.39. Found: C, 35.46; H, 5.37; N, 12.33.

1-[2-(N-Methylcarbamoyloxy)ethyl]-1*H*-imidazole (2c) To an ice-cooled solution of 1-(2-hydroxyethyl)-1*H*-imidazole (3.48 g, 31 mmol) and methyl isocyanate (5.5 mL, 93 mmol) in dry CH₂Cl₂ (10 mL) were added a few drops of Bu₂Sn(OAc)₂. The mixture was stirred at room temperature for 2 h and the solvent was evaporated to dryness to give a crude yellow solid. Purification of the crude product by flash column chromatography on silica gel (CHCl₃-MeOH, 9:1) afforded **2c** (4.48 g, 85%) as a white solid from EtOAc: mp 121.5-122.5 °C; *R*_f = 0.37 (CHCl₃-MeOH, 9:1); IR (KBr) *v*_{max} 3115, 1722 cm⁻¹; ¹H NMR (CDCl₃) δ 7.47 (s, 1 H), 7.04 (s, 1 H), 6.94 (s, 1 H), 5.68 (br s, 1 H), 4.31 (t, 2 H, *J* = 5.1 Hz), 4.17 (t, 2 H, *J* = 5.1 Hz), 2.77 (d, 3 H, *J* = 4.8 Hz); ¹³C NMR (CDCl₃) δ 156.35, 137.34, 129.30, 118.97, 63.30, 46.21, 27.30. Anal. Calcd for C₇H₁₁N₃O₂: C, 49.70; H, 6.55; N, 24.84. Found: C, 49.79; H, 6.59; N, 24.88.

3-Methyl-1-[2-(N-methylcarbamoyloxy)ethyl]-1*H*-imidazolium Iodide (2d)
(PN-II-184, BN 34812)

Following the general procedure for quaternization, the reaction of **2c** (1.44 g, 8.5 mmol) and methyl iodide (1.64 mL, 25.5 mmol) in THF

(10 mL) and CH₃CN (4 mL) at room temperature gave **2d** (2.15 g, 81%) as white needles from acetone/ether: mp 104-105 °C; IR (KBr) ν_{max} 3248, 3145, 3115, 1710 cm⁻¹; ¹H NMR (DMSO-d₆ + CDCl₃) δ 9.63 (s, 1 H), 7.79 (s, 1 H), 7.61 (s, 1 H), 6.70 (br s, 1 H), 4.59 (dd, 2 H, J = 4.5, 5.1 Hz), 4.37 (dd, 2 H, J = 4.5, 5.1 Hz), 4.10 (s, 3 H), 2.70 (d, 3 H, J = 8.1 Hz); ¹³C NMR (DMSO-d₆ + CDCl₃) δ 155.11, 136.26, 122.56, 122.30, 61.09, 48.42, 35.89, 26.15. Anal. Calcd for C₈H₁₄N₃O₂: C, 30.88; H, 4.54; N, 13.51. Found: C, 30.95; H, 4.55; N, 13.52.

1-[3-(N-Methylcarbamoyloxy)propyl]-1H-imidazole (3e) Carbamoylation of **3b** (2.16 g, 16.64 mmol) with methyl isocyanate (2.97 mL, 50 mmol) as described for **2c** gave a thick oil. Purification of the crude product by column chromatography on silica gel (CHCl₃-MeOH, 9:1) gave **3e** (3.07 g, 98%), as white crystals from EtOAc/hexane: mp 61-62.5 °C; R_f = 0.24 (CHCl₃-MeOH, 9:1); IR (KBr) ν_{max} 1079 cm⁻¹; ¹H NMR (CDCl₃) δ 7.48 (s, 1 H), 7.05 (s, 1 H), 6.93 (s, 1 H), 5.39 (br s, 1 H), 4.02-4.08 (m, 4 H), 2.78 (d, 3 H, J = 5.1 Hz), 2.04-2.12 (m, 2 H); ¹³C NMR (CDCl₃) δ 156.74, 136.95, 129.25, 118.67, 60.93, 43.49, 30.48, 27.24. Anal. Calcd for C₈H₁₃N₃O₂: C, 52.45; H, 7.15; N, 22.93. Found: C, 52.29; H, 7.17; N, 22.77.

3-Methyl-1-[3-(N-methylcarbamoyloxy)propyl]-1H-imidazolium Iodide (3f) (PN-II-178, BN34803) Following the general procedure for quaternization, the reaction of **3e** (1.83 g, 10 mmol) with methyl iodide in dry THF (15 mL) gave **3f** (2.86 g, 88%) as white needles from acetone/ether: mp 82-82.5 °C; IR (KBr) ν_{max} 3076, 1709 cm⁻¹; ¹H NMR (DMSO-d₆) δ 9.11 (s, 1 H), 7.76 (s, 1 H), 7.70 (s, 1 H), 6.91 (br s, 1 H), 4.21 (t, 2 H, J = 6.4 Hz), 3.95 (t, 2 H, J = 6.1 Hz), 3.84 (s, 3 H), 2.54 (d, 3 H, J = 4.8 Hz), 2.05-2.12 (m, 2 H); ¹³C NMR (DMSO-d₆) δ 156.45, 136.64, 123.60, 122.26, 60.54, 46.16, 35.81, 29.08, 26.91. Anal. Calcd for C₉H₁₆N₃O₂: C, 33.25; H, 4.96; N, 12.92. Found: C, 33.25; H, 4.94; N, 12.87.

1-Methyl-2-hydroxymethyl-1H-imidazole (4a) (12) 1-Methyl-1H-imidazole (10.9 mL, 0.136 mol) and formaldehyde (37% in water, 18.4 mL, 1.5 equiv) were heated in a pressure bottle for 5 h at 140 °C. The excess water and formaldehyde was removed under reduced pressure and the crude product **4a** obtained as a yellowish oil was used for next reaction without further purification.

1-Methyl-2-(N,N-dimethylcarbamoyloxy)methyl-1H-imidazole (4b) To a solution of **4a** in THF were added N,N-dimethylcarbamoyl chloride (6.3 mL, 0.68 mol) and triethylamine (9.5 mL, 0.68 mol). The mixture was refluxed for 16 h. The solvent was removed and the residue was partitioned between water and methylene chloride. The aqueous layer was washed with methylene chloride and the combined organic layer was evaporated to give the crude product **4b** as a thick oil.

1-Methyl-2-(N,N-dimethylcarbamoyloxy)methyl-1H-imidazole Hydrochloride (4c) (KC005, BM14299) **4b** was dissolved in ether and HCl gas was introduced. After reflux for 1 h a solid precipitate was obtained. The hydrochloride was recrystallized from ethanol/ether to give **4c** as white needle crystals: mp 161-3 °C; IR (KBr) ν_{\max} 3405, 3141, 3066, 2935, 1712, 1534, 1400, 1185 cm^{-1} ; ^1H NM (D_2O) δ 7.41 (s, 2 H), 5.34 (s, 2 H), 3.88 (s, 3 H), 2.92 (s, 3 H), 2.85 (s, 3 H). Anal. Calcd for $\text{C}_8\text{H}_{14}\text{ClN}_3\text{O}_2$: C, 43.74; H, 6.42; N, 19.13; Cl, 16.10. Found: C, 43.60; H, 6.40; N, 19.04; Cl, 16.03.

1-Methyl-2-(2-hydroxyethyl)-1H-imidazole (5a) A solution of *n*-BuLi in hexane (44 mL, 0.11 mol) was added dropwise via a canula to an ice-cooled (-5 °C) solution of 1-methylimidazole (8.21 g, 0.1 mol, colorless liquid, bp 47°C/0.3mmHg) in dry THF (200 mL). The mixture was stirred at 0 °C for 1 h, then ethylene oxide (6.61 g) was slowly added. The mixture was allowed to gradually warm to room temperature and was stirred overnight. The reaction mixture was quenched with cold 10% HCl solution (200 mL). The organic layer was washed with 10% HCl solution (2 x 30 mL). The combined aqueous layers were basified with K_2CO_3 , saturated with NaCl and then extracted with CHCl_3 (6 x 50 mL). The combined organic layers were washed with brine and dried (MgSO_4). Evaporation of the solvent gave a thick yellow oil. Removal of unreacted starting material (2.9 g) by vacuum distillation (Kugelrohr) afforded **5a** as a yellow solid (4.68 g, 57% conversion): ^1H NMR (CDCl_3) δ 6.89 (s, 1 H), 6.80 (s, 1 H), 4.00 (t, 2 H, $J = 5.6$ Hz), 3.57 (s, 3 H), 2.84 (t, 2 H, $J = 5.6$ Hz); ^{13}C NMR (CDCl_3) δ 146.7, 126.6, 120.3, 59.7, 32.4, 28.9.

1-Methyl-2-(2-N,N-dimethylcarbamoyloxyethyl)-1H-imidazole (5b) NaH (1.1 g, 36.6 mmol, 80% dispersion in mineral oil) was carefully added to a mixture of **5a** (4.2 g, 33.3 mmol) in dry DMF (50 mL) at 0 °C. After being stirred for 10 min in an ice-

bath, then 30 min at room temperature, the mixture was cooled to 0 °C and N,N-dimethylcarbamoyl chloride (4.65 g, 43 mmol) was slowly added by syringe. The ice-bath was removed and the reaction mixture was stirred at room temperature overnight. The mixture was quenched with 1% KOH solution, saturated with NaCl and then extracted with CHCl₃ (5 x 50 mL). The organic extract was washed with 5% HCl solution (2 x 150 mL). The cooled combined aqueous layers were basified with 10% KOH solution, saturated with NaCl and then extracted with CHCl₃ (6 x 50 mL). The organic phase was dried (MgSO₄) and evaporated to dryness to give a thick oil **5b** (3.76 g, 57%): ¹H NMR (CDCl₃) δ 6.89 (s, 1 H), 6.77 (s, 1 H), 4.36 (t, 2 H, J = 7.2 Hz), 3.58 (s, 3 H), 2.99 (t, 2 H, J = 7.2 Hz), 2.84 (br s, 6 H).

1,3-Dimethyl-2-(2-N,N-dimethylcarbamoyloxyethyl)-1H-imidazolium Tosylate (5c) (PN68, BM16186) A mixture of **5b** (0.3 g, 1.57 mmol) and methyl *p*-toluenesulfonate (0.44 g, 2.35 mmol) in dry CH₃CN (10 mL) was stirred at 60 °C (bath temperature) for 14 h. The reaction mixture was diluted with CH₃CN and decolorized with charcoal. The volume of organic solvent was reduced under aspirator pressure then ether was added. The resulting mixture was cooled in the freezer to give a crude solid **5c** (0.48 g, 67%) as white crystals from CH₃CN/ether: mp 145- 145.5 °C; IR (KBr) ν_{max} 3173, 3088, 1695, 1207 cm⁻¹; ¹H NMR (CDCl₃) δ 7.67 (d, 2 H, J = 8.0 Hz), 7.53 (s, 2 H), 7.11 (s, 2 H, J = 8.0 Hz), 4.26 (t, 2 H, J = 6.3 Hz), 3.82 (s, 6 H), 3.42 (t, 2 H, J = 6.3 Hz), 2.81 (s, 3 H), 2.76 (s, 3 H), 2.32 (s, 3 H); ¹³C NMR (CDCl₃) δ 155.25, 144.06, 143.89, 138.75, 128.30, 125.48, 122.89, 60.47, 36.27, 35.70, 35.12, 23.81, 20.99. Anal. Calcd for C₁₇H₂₅N₃O₅S: C, 53.25; H, 6.57; N, 10.96. Found: C, 53.16; H, 6.59; N, 10.94.

1-Methyl-2-[2-(N-methylcarbamoyloxy)ethyl]-1H-imidazole (5d) 1-Methyl-2-(2-hydroxyethyl)-1H-imidazole (**13**) (3.4 g, 26.9 mmol) was carbamoylated with methyl isocyanate (8 mL, 134 mmol) as described for **2c** gave a dark yellow oil. Purification of the crude product by column chromatography on silica gel (CHCl₃-MeOH, 9:1) yielded **5d** (2.526 g, 51%) as white needles from CH₂Cl₂/hexane: mp 125 - 125.5 °C; R_f = 0.32 (CHCl₃-MeOH, 9:1); ¹H NMR (CDCl₃) δ 6.83 (s, 1 H), 6.72 (s, 1 H), 5.39 (br s, 1 H), 4.31 (t, 2 H, J = 7.0 Hz), 3.53 (s, 3 H), 2.93 (t, 2 H, J = 7.0 Hz), 2.69 (d, 3 H, J = 4.8 Hz); ¹³C NMR (CDCl₃) δ 156.93, 144.70, 127.09,

120.61, 62.32, 32.46, 27.19, 26.77. Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.93. Found: C, 52.47; H, 7.17; N, 23.01.

1,3-Dimethyl-2-[2-(N-methylcarbamoyloxy)ethyl]-1H-imidazolium Iodide (5e)
(PN-II-68, BM18975)

Following the general procedure for Quaternization, the reaction of **5d** (0.46 g, 2.5 mmol) with methyl iodide (0.3 mL, 5 mmol) gave a white solid **5e** (0.76 g, 93%): mp 142-143 °C from MeOH/Et₂O; IR (KBr)_{vmax} 3315, 3117, 3090, 1724 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.65 (s, 2 H), 7.06 (br m, 1 H), 4.19 (t, 2 H, J = 5.9 Hz), 3.79 (s, 6 H), 3.34 (t, 2 H, J = 5.9 Hz), 2.46 (d, 3 H, J = 5.1 Hz); ¹³C NMR (DMSO-d₆) δ 155.84, 144.24, 122.59, 59.92, 35.03, 26.79, 23.29. Anal. Calcd for $C_9H_{16}IN_3O_2$: C, 33.25; H, 4.96; N, 12.92. Found: C, 33.33; H, 4.96; N, 12.98.

1-Methyl-2-(3-hydroxypropyl)-1H-imidazole (6a) To a cooled (-5 °C) solution of 1,2-dimethylimidazole (10.48 g, 0.109 mol) in dry THF (250 mL) was added dropwise a solution of *n*-BuLi in hexane (48 mL, 0.12 mol). The rate of addition was such that the temperature of the mixture remained <0 °C. The mixture was stirred at this temperature for 30 min, then ethylene oxide (6 mL, 0.12 mol) was added at such a rate that the temperature of the mixture was below 10 °C. After being stirred at this temperature for an additional 1 h, then at room temperature overnight, the reaction mixture was quenched with 10% HCl solution (300 mL). The organic layer was washed with 10% HCl solution (2 x 50 mL). The combined aqueous layers were basified with K₂CO₃, then extracted with CHCl₃ (8 x 50 mL). The organic phase was dried (MgSO₄) and evaporated to dryness to give a thick yellow oil **6a** (13 g, 85%): ¹H NMR (CDCl₃) δ 6.9 (s, 1 H), 6.76 (s, 1 H), 4.14 (t, 2 H, J = 6.3 Hz), 3.55 (s, 3 H), 2.87 (s, 3 H), 2.72 (t, 2 H, J = 7.6 Hz), 2.06-2.16 (m, 2 H).

1-Methyl-2-(3-N,N-dimethylcarbamoyloxypropyl)-1H-imidazole (6b) N,N-Dimethylcarbamoyl chloride (3.68 g, 34.2 mmol) was added via a syringe to a solution of **6a** (3.2 g, 22.8 mmol) in dry pyridine (20 mL). The reaction mixture was heated to gentle reflux for 30 h, then cooled to room temperature. Water (30 mL) was added and the mixture was stirred for 10 min. The aqueous phase was basified with K₂CO₃, saturated with NaCl, then extracted with CHCl₃ (6 x 25 mL). The combined organic layers were washed with brine, dried (MgSO₄) and decolorized with charcoal. Removal of the solvent gave a brown oil **6b** (3.5 g, 73%): ¹H NMR (CDCl₃) δ 6.9

(s, 1 H), 6.77 (s, 1 H), 4.15 (t, 2H, $J = 6.3$ Hz), 3.55 (s, 3 H), 2.88 (br s, 6 H), 2.72 (t, 2 H, $J = 7.5$ Hz), 2.07-2.16 (m, 2 H).

1,3-Dimethyl-2-(3-*N,N*-dimethylcarbamoyloxypropyl)-1*H*-imidazolium Tosylate (6c) (PN38, BM16177) Quaternization of **6b** (2.03 g, 9.6 mmol) was carried out with MeOTs (2.68 g, 14.4 mmol) in CH_3CN (25 mL) to give **6c** (1.75 g, 46%) as colorless needles from CH_3CN /ether: mp 124.5°-125.5 °C; IR (KBr) ν_{max} 3115, 3082, 1709, 1215, 1182 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.67 (d, 2 H, $J = 8.1$ Hz), 7.54 (s, 2 H), 7.11 (d, 2 H, $J = 8.1$ Hz), 4.04 (t, 2 H, $J = 5.8$ Hz), 3.82 (s, 6 H), 3.11 (t, 2 H, $J = 7.6$ Hz), 2.86 (s, 3H), 2.79 (s, 3 H), 2.32 (s, 3 H), 1.93 (m, 2H); ^{13}C NMR (CDCl_3) δ 155.76, 146.17, 144.18, 138.80, 128.35, 125.59, 122.81, 63.41, 36.29, 35.72, 35.11, 25.83, 21.07, 20.12. Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{N}_3\text{O}_5\text{S}$: C, 54.39; H, 6.85; N, 10.57; S, 8.06. Found: C, 54.21; H, 6.92; N, 10.52; S, 7.99.

1-Methyl-2-[3-(*N*-methylcarbamoyloxy)propyl]-1*H*-imidazole (6d) 1-Methyl-2-(3-hydroxypropyl)-1*H*-imidazole (**14**) (3.67 g, 26.2 mmol) was carbamoylated as described for **2c** with methyl isocyanate (7.8 mL, 131 mmol) in the presence of a catalytic amount of $\text{Bu}_2\text{Sn}(\text{OAc})_2$ in dry CH_2Cl_2 (25 mL) to give **6d** as a dark brown oil (4.68 g, 91%): ^1H NMR (CDCl_3) δ 6.92 (s, 1 H), 6.79 (s, 1 H), 4.63 (br s, 1 H), 4.15 (t, 2H, $J = 6.2$ Hz), 3.57 (s, 3 H), 2.79 (d, 3 H, $J = 4.8$ Hz), 2.73 (t, 2 H, $J = 7.6$ Hz), 2.13 (m, 2 H).

1,3-Dimethyl-2-[3-(*N*-methylcarbamoyloxy)propyl]-1*H*-imidazolium Iodide (6e) (PN-II-62, BM18966) Following the general procedure for Quaternization, the reaction of **6d** (4.15 g, 21 mmol) with methyl iodide (2.6 mL, 42 mmol) in THF (20 mL) gave **6e** (6.6 g, 92%), as white needles from MeOH/ Et_2O : mp 146-147 °C; IR (KBr) ν_{max} 3289, 3115, 3088, 1723, 1248, 1141 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 7.60 (s, 2 H), 6.89 (br m, 1 H), 3.93 (t, 2 H, $J = 6.0$ Hz), 3.76 (s, 6 H), 3.03 (t, 2 H, $J = 7.6$ Hz), 2.50 (d, 3 H, $J = 4.5$ Hz), 1.83-1.90 (m, 2 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 156.38, 146.16, 122.33, 62.34, 34.82, 26.82, 25.19, 19.38. Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{IN}_3\text{O}_2$: C, 35.41; H, 5.35; N, 12.39. Found: C, 35.25; H, 5.42; N, 12.32.

1-Methyl-2-phenylthio-5-[(*N,N*-dimethylcarbamoyloxy)methyl]-1*H*-imidazole (7a) To a cooled solution (-78 °C) of 1-methyl-2-phenylthio-1*H*-imidazole (**4**) (1.9 g,

10 mmol) in dry THF (40 mL) was added dropwise a solution of *n*-BuLi in hexane (4 mL, 10 mmol). The mixture was stirred for 30 min, then predried paraformaldehyde (0.45 g, 15 mmol) was added. The mixture was stirred at -78 °C for 15 min and allowed to warm up slowly. The temperature of the reaction mixture was maintained at 10-15 °C using an ice bath until the color of the mixture changed from orange to milky white (about 30 min). The reaction mixture was then cooled to 0 °C and *N,N*-dimethylcarbamoyl chloride (1.6 g, 15 mmol) was added dropwise. The mixture was stirred at room temperature for 1 h then quenched with cold aqueous solution of 10% HCl (40 mL) and extracted with ether (2 x 15 mL). The aqueous phase was basified with 20% KOH solution, saturated with NaCl and extracted with EtOAc (6 x 50 mL). The organic layers were washed with brine and dried (Na₂SO₄). Removal of solvent gave **7a** (2.5 g, 86%) as a thick oil: ¹H NMR (CDCl₃) δ 7.18-7.30 (m, 6 H), 5.10 (s, 2 H), 3.63 (s, 3 H), 2.93 (s, 3 H), 2.86 (s, 3 H).

1-Methyl-5-[(*N,N*-dimethylcarbamoyloxy)methyl]-1*H*-imidazole (7b) A mixture of **7a** (1.17 g, 4 mmol) and Raney Nickel (ca. 4.7 g, W-2 in ethanol) in ethanol/acetone was stirred at room temperature for 15 min. The solvent was carefully decanted and the solid nickel residue was washed with EtOH (2x50 mL), then CH₂Cl₂ (2 x 50 mL). The combined organic phase was evaporated to dryness to give a residue which was redissolved in CHCl₃. The mixture was dried (MgSO₄) and filtered (Celite). Removal of solvent gave **7b** (0.414 g, 56%) as colorless solid: ¹H NMR (CDCl₃) δ 7.45 (s, 1 H), 7.10 (s, 1 H), 5.10 (s, 2 H), 3.67 (s, 3 H), 2.93 (s, 3 H), 2.87 (s, 3 H).

1,3-Dimethyl-4-[(*N,N*-dimethylcarbamoyloxy)methyl]-1*H*-imidazolium Iodide (7c) (PN-177, BM17816) A mixture of **7b** (0.36 g, 1.96 mmol) and methyl iodide (0.97 mL, 15 mmol) in dry THF (8 mL) was stirred at 60 °C for 2 h. The solvent was then removed under reduced pressure. The resulting yellow oil was dissolved in H₂O (5 mL). The aqueous solution was then washed with CHCl₃ (3 x 4 mL), ether (4 mL) and evaporated to dryness to afford a thick, yellow oil **7c** (0.8 g, 82%) which gave a white solid on crystallization with acetone/ether: mp 105.5 - 6.5 °C; IR (KBr) ν_{max} 3109, 3061, 1709, 1188 cm⁻¹; ¹H NMR (DMSO) δ 9.14 (s, 1 H), 7.80 (s, 1 H), 5.14 (s, 2 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 2.83 (s, 3 H), 2.81 (s, 3 H); ¹³C NMR (DMSO) δ

154.60, 137.81, 129.82, 123.29, 54.68, 36.16, 35.89, 35.60, 33.79. Anal. Calcd for $C_9H_{16}O_2N_3I$: C, 33.25; H, 4.96; N, 12.92. Found: C, 33.31; H, 4.94; N, 12.83.

1-Methyl-2-phenylthio-5-[2-(N,N-dimethylcarbamoyloxy)ethyl]-1H-imidazole

(8a) *n*-BuLi in hexane (4.4 mL, 11 mmol) was added to a solution of 1-methyl-2-phenylthio-1H-imidazole (1.9 g, 10 mmol) in dry THF (50 mL) at -78 °C. The mixture was stirred for 30 min, then pre-cooled ethylene oxide (0.9 g, 20 mmol) was added. After being allowed to warm to room temperature overnight the reaction mixture was cooled in an ice-bath, then N,N-dimethylcarbamoyl chloride (1.61 g, 15 mmol) was added via a syringe. The mixture was stirred at room temperature for 14 h, then diluted with ether (20 mL) and quenched with cold 10% HCl solution. The organic phase was separated and washed with 10% HCl solution (2 x 15 mL). The combined aqueous layers were basified with cold 20% KOH solution to pH = 10, and extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of solvent gave **8a** (2.9 g, 95%) as a thick oil: 1H NMR ($CDCl_3$) δ 7.11-7.28 (m, 5 H), 7.04 (s, 1 H), 4.29 (t, 2 H, J = 6.9 Hz), 3.56 (s, 3 H), 2.8-2.95 (overlapped m, 8 H).

1-Methyl-5-[2-(N,N-dimethylcarbamoyloxy)ethyl]-1H-imidazole (8b)

Desulfurization of **8a** (1.5 g, 5 mmol) with Raney Ni (ca. 5.8 g, W-2 in ethanol) in absolute EtOH (30 mL) following the procedure described for **7a** gave **8b** (0.84 g, 85%) as an oil: 1H NMR ($CDCl_3$) δ 7.39 (s, 1 H), 6.87 (s, 1 H), 4.27 (t, 2 H, J = 6.9 Hz), 3.60 (s, 3 H), 2.84-2.93 (overlapped m, 8 H); ^{13}C NMR ($CDCl_3$) δ 156.27, 137.77, 128.04, 127.26, 63.29, 36.34, 35.81, 31.21, 24.06.

1,3-Dimethyl-4-[2-(N,N-dimethylcarbamoyloxy)ethyl]-1H-imidazolium Iodide (8c) (PN-294, BM17843)

Quaternization of **8b** (0.33 g, 1.67 mmol) was carried out with methyl iodide (0.83 mL, 13.4 mmol) in THF (5 mL) to give **8c** as a thick, pale yellow oil: 1H NMR ($DMSO-d_6$) δ 8.98 (s, 1 H), 7.54 (s, 1 H), 4.20 (t, 2 H, J = 6.4 Hz), 3.81 (s, 3 H), 3.77 (s, 3 H), 2.99 (t, 2 H, J = 6.4 Hz), 2.81 (s, 6 H); ^{13}C NMR ($DMSO-d_6$) δ 155.27, 136.63, 131.89, 120.68, 61.86, 36.00, 35.70, 35.55, 33.31. Anal. Calcd for $C_{10}H_{18}O_2N_3I \cdot 1/2H_2O$: C, 34.49; H, 5.50; N, 12.06. Found: C, 34.48; H, 5.51; N, 11.97.

1-Methyl-2-phenylthio-5-(3-hydroxypropyl)-1*H*-imidazole (9a) To a solution of 1-methyl-2-phenylthio-1*H*-imidazole (4.1 g, 21.54 mmol) in dry THF (45 mL) at -78 °C was added dropwise a solution of *n*-BuLi in hexane (9.05 mL, 22.62 mmol). After being stirred at -78 °C for 30 min, the mixture was added via canula to a precooled (-78 °C) solution of oxetane (1.25 g, 21.5 mmol) and BF₃-OEt₂ (3.97 mL, 32.3 mmol) in dry THF (50 mL). The reaction mixture was stirred at -78 °C for 2 h and warmed up to room temperature overnight. Work up as usual gave a crude product **9a** (2.37 g, 44%) as a dark yellow oil: ¹H NMR (CDCl₃) δ 7.01-7.28 (m, 5 H), 6.93 (s, 1 H), 3.71 (t, 2 H, J = 6.2 Hz), 3.49 (s, 3 H), 3.26 (br s, 1 H), 2.65 (t, 2 H, J = 7.9 Hz), 1.89 (m, 2 H); ¹³C NMR (CDCl₃) δ 129.16, 127.48, 127.01, 125.94, 61.17, 31.02, 30.63, 21.48.

1-Methyl-2-phenylthio-5-[3-(*N,N*-dimethylcarbamoyloxy)propyl]-1*H*-imidazole. (9b) To a cooled (-78 °C) solution of **9a** (1.66 g, 6.71 mmol) in dry THF (40 mL) was added dropwise a solution of *n*-BuLi in hexane (2.95 mL, 7.4 mmol). The mixture was stirred at -78 °C for 30 min. Then a solution of *N,N*-dimethylcarbamoyl chloride (0.82 mL, 8.7 mmol) in THF (10 mL) was added slowly. After 15 min the reaction mixture was allowed to warm to room temperature and was heated to gentle reflux for 30 min. The mixture was cooled to room temperature, carefully basified to pH=10 using aqueous 20% NaOH solution, saturated with NaCl and extracted with CHCl₃ (5 x 30 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄) and filtered. The brown filtrate was evaporated to dryness to give a brown oil. Purification of the crude product by column chromatography on silica gel (CHCl₃-MeOH, 9:1) afforded **9b** (1.12 g, 52%) as an oil: R_f = 0.6 (CHCl₃-MeOH); ¹H NMR (CDCl₃) δ 7.11-7.27 (m, 5 H), 6.98 (s, 1 H), 4.16 (t, 2 H, J = 6.3 Hz), 3.52 (s, 3 H), 2.97 (br s, 6 H), 2.64 (t, 2 H, J = 7.7 Hz), 1.96-2.05 (m, 2 H); ¹³C NMR (CDCl₃) δ 156.00, 136.52, 134.91, 134.51, 128.78, 127.20, 126.99, 125.95, 63.88, 38.16, 35.97, 35.45, 30.66, 27.04, 21.43.

1-Methyl-5-[3-(*N,N*-dimethylcarbamoyloxy)propyl]-1*H* -imidazole (9c) Desulfurization of **9b** (0.85 g, 2.68 mmol) with Raney Nickel (3.15 g, 53.6 mmol) in EtOH as described previously gave **9c** (0.214 g, 37.8%) as a pale yellow oil: ¹H NMR (CDCl₃) δ 7.37 (s, 1 H), 6.79 (s, 1 H), 4.15 (t, 2 H, J = 6.3 Hz), 3.56 (s, 3 H), 2.91 (s,

6 H), 2.63 (t, 2 H, $J = 7.6$ Hz), 1.93-2.02 (m, 2 H); ^{13}C NMR (CDCl_3) δ 156.19, 137.28, 130.82, 125.90, 64.08, 36.07, 35.52, 30.85, 27.59, 20.22.

1,3-Dimethyl-4-[3-(*N,N*-dimethylcarbamoyloxy)propyl]-1*H*-imidazolium Iodide (9d) (PN-I-292, BM19070) Quaternization of **9c** (95 mg, 0.45 mmol) with methyl iodide (0.14 mL, 2.25 mmol) in THF (3 mL) gave a white solid **9d** (134 mg, 85%): mp 115-6 °C from acetone/ether; IR (KBr) ν_{max} 3172, 1701, 1188 cm^{-1} ; ^1H NMR (CDCl_3) δ 10.00 (s, 1 H), 7.22 (s, 1 H), 4.18 (t, 2 H, $J = 6.2$ Hz), 4.04 (s, 3 H), 3.96 (s, 3 H), 2.74 (t, 2 H, $J = 7.5$ Hz), 1.99-2.09 (m, 2 H); ^{13}C NMR (CDCl_3) δ 137.30, 135.06, 119.86, 63.28, 36.83, 36.45, 36.01, 34.21, 28.82, 20.23. Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{O}_2\text{N}_3\text{I}$: C, 37.40; H, 5.70; N, 11.89. Found: C, 37.45; H, 5.74; N, 11.81.

Imidazo[1,2-*a*]pyridin-5-ol (10a) A mixture of 2,6-diaminopyridine (10.9 g, 0.1 mol) and chloroacetaldehyde (17.5 g, 45% w/w in water, 0.1 mol) in acetone (200 mL) was refluxed overnight. The reaction mixture was cooled and filtered to give a solid, which was washed with several portions of fresh acetone and dried under vacuum to afford 5-aminoimidazo[1,2-*a*]pyridine hydrochloride (16.9 g, 100%) as tan solid: ^1H NMR ($\text{DMSO}-d_6$) δ 8.45 (d, 1 H, $J = 2.4$ Hz), 8.08 (d, 1 H, $J = 2.4$ Hz), 7.99 (br s, 2 H), 7.69 (dd, 1 H, $J = 7.8, 8.4$ Hz), 7.00 (d, 1 H, $J = 8.4$ Hz), 6.49 (d, 1 H, $J = 7.8$ Hz). A mixture of 5-aminoimidazo[1,2-*a*]pyridine hydrochloride (16.6 g, 97.8 mmol) in 70% H_2SO_4 solution was stirred at 120 °C (oil bath temperature) for 10 h. The reaction mixture was cooled and carefully neutralized with an aqueous 20% NaOH solution. Filtration of the mixture gave **10a** (10.93 g, 75.4%) as an olive green solid: $R_f = 0.53$ (CHCl_3 -MeOH, 9:1); ^1H NMR ($\text{DMSO}-d_6$) δ 7.64 (d, 1 H, $J = 2.1$ Hz), 7.53 (d, 1 H, $J = 2.1$ Hz), 7.34 (dd, 1 H, $J = 8.1, 8.4$ Hz), 6.15 (d, 1 H, $J = 8.1$ Hz), 5.63 (d, 1 H, $J = 8.4$ Hz), 1.82 (br s, 1 H).

1-Methylimidazo[1,2-*a*]pyridin-5-one (10b) A mixture of **10a** (2.68 g, 20 mmol) and sodium amide (1.09 g, 28 mmol) in dry DMF (30 mL) was stirred at room temperature for 30 min. Methyl iodide (1.62 mL, 26 mmol) was added dropwise by syringe and the mixture was stirred at room temperature for 2 h. Solvent was evaporated to dryness under vacuum and the resulting residue was partitioned between a sat'd NaHCO_3 solution and CHCl_3 . Insoluble material was removed by

filtration. The aqueous phase was extracted with CHCl_3 (5 x 50 mL). The organic layers were washed with brine (2 x 50 mL), dried (anhydrous Na_2SO_4) and filtered. Removal of solvent yielded a crude product which was purified by column chromatography (silica gel, 5% of MeOH in CHCl_3) to afford **10b** (1.44 g, 48.6 %) as an off-white solid from acetone/hexane: mp 70-72 °C; R_f = 0.38 (CHCl_3 -MeOH, 19:1); ^1H NMR (CDCl_3) δ 7.74 (d, 1 H, J = 2.4 Hz), 7.44 (t, 1 H, J = 8.4 Hz), 6.97 (d, 1 H, J = 2.4 Hz), 6.01 (d, 2 H, J = 8.4 Hz), 3.68 (s, 3 H); ^{13}C NMR (CDCl_3) δ 156.97, 142.44, 136.98, 120.24, 108.46, 99.41, 83.47, 32.85.

1-Methyl-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Chloride (10c) (PN-III-220, BN38865) To a mixture of **10b** (1.0 g, 6.8 mmol) in dry THF (15 mL) and HMPT (2.35 mL, 13.5 mmol) was added slowly N,N-dimethylcarbamoyl chloride (1.24 mL, 13.5 mmol). The reaction mixture was stirred at 60 °C overnight, then cooled in an ice bath. Solvent was carefully removed by pipette and the solid was washed with ether and dried. Recrystallization of the crude in CH_3CN /ether gave **10c** (1.38 g, 80 %) as a gray solid: mp 149-151 °C; ^1H NMR (CDCl_3) δ 8.90 (d, 1 H, J = 2.0 Hz), 8.12 (d, 1 H, J = 2.0 Hz), 8.07 (d, 1 H, J = 9.0 Hz), 8.00 (dd, 1 H, J = 7.7, 9.0 Hz), 7.32 (d, 1 H, J = 7.7 Hz), 4.42 (s, 3 H), 3.29 (s, 3 H), 3.12 (s, 3 H). Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{ClN}_3\text{O}_2$: C, 51.67; H, 5.52; Cl, 13.86; N, 16.43. Found: C, 51.43; H, 5.59; Cl, 13.73; N, 16.34.

2-Methyl-5-aminoimidazo[1,2-a]pyridine (11a) To a mixture of 2,6-diaminopyridine (10.9 g, 0.1 mol) in absolute ethanol (100 mL) at 70 °C was added dropwise a solution of chloroacetone (7.96 mL, 0.1 mol) in absolute ethanol (30 mL). The mixture was gently refluxed overnight. Additional chloroacetone (2 mL) was added and the mixture was refluxed for 5 h. The solvent was reduced to 1/3 of its original volume and Et_2O was added. The mixture was cooled in an ice bath to give a solid which was dissolved in water and neutralized with a saturated NaHCO_3 solution. The volume of water was reduced to give **11a** (7.2 g, 48.6%) as black solid: mp 155-156.5 °C; R_f = 0.17 (CHCl_3 -MeOH, 9:1); ^1H NMR ($\text{DMSO}-d_6$) δ 7.52 (s, 1 H), 7.02 (dd, 1 H, J = 7.4, 8.7 Hz), 6.68 (d, 1 H, J = 8.7 Hz), 6.45 (br s, 2 H), 5.89 (dd, 1 H, J = 0.8, 7.4 Hz), 2.29 (d, 3 H, J = 0.8 Hz); ^{13}C NMR ($\text{DMSO}-d_6$) δ 145.79, 142.00,

141.29, 126.33, 104.22, 102.13, 89.48, 14.39. Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.02; H, 6.15; N, 28.28.

2-Methyl-5-hydroxyimidazo[1,2-a]pyridine (11b) Following the general procedure for preparation of 5-hydroxyimidazo[1,2-a]pyridine, **11a** (3.4 g, 23.1 mmol) gave **11b** (2.64 g, 77.2%): $R_f = 0.39$ ($CHCl_3$ -MeOH, 9:1); 1H NMR (DMSO- d_6) δ 7.38 (s, 1 H), 7.28 (dd, 1 H, $J = 7.8, 8.4$ Hz), 6.08 (d, 1 H, $J = 7.8$ Hz), 5.60 (d, 1 H, $J = 8.4$ Hz); ^{13}C NMR (DMSO- d_6) δ 155.55, 142.21, 135.89, 127.85, 105.04, 97.00, 84.52, 10.25.

General Procedure for Carbamoylation of 5-Hydroxyimidazo[1,2-a]pyridine Derivatives A mixture of 5-hydroxyimidazo[1,2-a]pyridine derivative (1 equiv) and sodium hydride (1.5 equiv) in dry DMF was stirred at room temperature for 30 min, then at 50 °C for 30 min. N,N-dimethylcarbamoyl chloride (1.5 equiv) was added slowly by syringe and the reaction mixture was stirred at 80 °C for 10 h. Solvent was evaporated under vacuum. The resulting residue was partitioned between an aqueous $NaHCO_3$ solution and $CHCl_3$. Insoluble material was removed by filtration. The aqueous phase was extracted with $CHCl_3$. The organic layers were washed with brine, dried (Na_2SO_4) and filtered. Removal of solvent gave a crude product which was purified by column chromatography.

General Procedure for Quaternization of Carbamoyloxyimidazo[1,2-a]pyridine Derivatives A mixture of carbamate and methyl iodide or methyl *p*-toluenesulfonate (1.5 equiv) in dry THF (or acetonitrile) was maintained at 60 °C overnight. Ether was then added and the reaction mixture was cooled in ice. The precipitate was collected and purified by recrystallization.

2-Methyl-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (11c) Following the general procedure for carbamoylation of 5-hydroxyimidazo[1,2-a]pyridine, **11b** (1.1 g, 7.4 mmol) gave a crude product which was purified by column chromatography (silica gel; gradient elution, 4 to 8% of MeOH in $CHCl_3$) to give **11c** (1.09 g, 67.3%) as an off-white solid from EtOAc/hexane: mp 110-111 °C; $R_f = 0.59$ ($CHCl_3$ -MeOH, 24:1); 1H NMR ($CDCl_3$) δ 7.38 (d, 1 H, $J = 8.7$ Hz), 7.27 (s, 1 H),

7.16 (dd, 1 H, $J = 7.5, 8.7$ Hz), 6.59 (d, 1 H, $J = 7.5$ Hz), 3.20 (s, 3 H), 3.06 (s, 3 H), 2.46 (s, 3 H); ^{13}C NMR (CDCl_3) δ 151.58, 146.43, 143.31, 140.14, 112.92, 104.83, 101.29, 36.90, 36.52, 14.27. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.25; H, 5.99; N, 19.06.

1,2-Dimethyl-5-(*N,N*-dimethylcarbamoyloxy)imidazo[1,2-*a*]pyridinium

***p*-Toluenesulfonate (11d) (PN-III-190, BN38856)** Following the general procedure for Quaternization, **11c** (1.2 g, 5.5. mmol) was reacted with methyl *p*-toluenesulfonate (1.52 g, 8.2 mmol) in dry THF (10 mL) to give **11d** (2.15 g, 96.8 %) as a white solid from CH_3CN /ether: mp 162-162.5 °C; IR (KBr) ν_{max} 3094, 1755, 1205, 1190, 1141 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.03 (s, 1H), 7.98 (d, 1 H, $J = 9.0$ Hz), 7.84 (dd, 1 H, $J = 7.8, 9.0$ Hz), 7.68 (d, 2 H, $J = 8.3$ Hz), 7.19 (d, 1 H, $J = 7.8$ Hz), 7.03 (d, 2 H, $J = 8.3$ Hz), 4.00 (s, 3 H), 3.23 (s, 3 H), 3.04 (s, 3 H), 2.54 (s, 3 H), 2.13 (s, 3 H); ^{13}C NMR (CDCl_3) δ 150.23, 144.44, 141.63 140.30, 138.49, 135.99, 134.23, 128.17, 125.79, 108.27, 107.51, 107.11, 37.35, 37.10, 31.67, 21.13, 9.95. Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_5\text{S}$: C, 56.28; H, 5.72; N, 10.36. Found: C, 56.40; H, 5.67; N, 10.44.

2-(2-Propyl)imidazo[1,2-*a*]pyridin-5-ol (12b) To a cooled mixture of sodium hydride (1.46 g, 61.0 mmol, washed with pentane twice) in dry DMF (30 mL) was added slowly a solution of 2-amino-6-hydroxypyridine (5) (4.77 g, 40 mmol) in dry DMF (30 mL). The mixture was stirred in the cooling bath for 15 min then warmed and stirred at room temperature for 3 h. A solution of 1-bromo-3-methylbutan-2-one (7.26 g, 44 mmol) in dry THF (20 mL) was added at once. The reaction mixture was stirred at 80 °C (oil bath temperature) overnight. Solvent was removed to dryness under reduced pressure. The resulting residue was partitioned between water and CHCl_3 . The aqueous phase was extracted with CHCl_3 (4 x 40 mL). The organic layers were washed with water, brine and dried (anhydrous Na_2SO_4). Removal of solvent gave a crude, which was purified by column chromatography (silica gel, CHCl_3 -MeOH, 9:1) to give **12b** (3.32 g, 47.1%) as a tan solid: mp 163-165 °C; $R_f = 0.5$ (CHCl_3 -MeOH, 9:1); ^1H NMR (CDCl_3) δ 7.51 (s, 1 H), 7.37 (t, 1 H, $J = 8.4$ Hz), 6.41 (d, 1 H, $J = 8.4$ Hz), 5.98 (d, 1 H, $J = 8.4$ Hz), 3.13 (septet, 1 H, $J = 6.9$ Hz), 1.39 (d, 6 H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3) δ 156.84, 142.73, 139.94, 136.05, 103.39, 97.32,

89.31, 25.90, 21.62. Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.87; H, 6.88; N, 15.65.

2-(2-Propyl)-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (12c) To an ice-cooled mixture of sodium hydride (0.5 g, 20.8 mmol, washed with pentane twice and dried under Ar) in dry THF (20 mL) was added via canula a solution of **12b** (2.64 g, 15 mmol) in dry THF (15 mL). The mixture was warmed up and stirred at 50 °C for 3 h. N,N-dimethylcarbamoyl chloride (2.07 mL, 22.5 mmol) was then added by syringe. After being stirred at 50 °C for 5 h, the reaction mixture was evaporated to dryness and the resulting residue was partitioned between water and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ (4 x 30 mL). The organic layers were washed with brine (2 x 30 mL), dried (anhydrous Na_2SO_4) and filtered. Evaporation of the solvent gave a crude which was purified by column chromatography (silica gel, 20% of hexane in EtOAc) to give **12c** (2.83 g, 76.3 %) as colorless needles from EtOAc/hexane: mp 91-92 °C; R_f = 0.5 (EtOAc-hexane, 9:1); 1H NMR ($CDCl_3$) δ 7.42 (dd, 1 H, J = 0.6, 9.0 Hz), 7.24 (s, 1 H), 7.17 (dd, 1 H, J = 7.5, 9.0 Hz), 6.58 (dd, 1 H, J = 0.6, 7.5 Hz), 3.23 (s, 3 H), 3.07-3.16 (overlapped m, 1 H), 3.08 (overlapped s, 3 H), 1.38 (d, 6 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 154.21, 151.81, 146.57, 140.48, 124.34, 113.36, 102.77, 101.28, 37.09, 36.72, 28.47, 22.41. Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.24; H, 6.97; N, 16.92.

1-Methyl-2-(2-propyl)-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Iodide (12d) (PN-IV-36, BN40490) Following the general procedure for Quaternization, **12c** (70 mg, 0.28 mmol) was treated with methyl iodide (excess) in THF (2 mL) to give **12d** (99 mg, 96 %) as white needles from CH_3CN/Et_2O : mp 155-6 °C; IR (KBr) ν_{max} 3103, 3053, 1749, 1141 cm^{-1} ; 1H NMR ($CDCl_3$) δ 8.23 (d, 1 H, J = 9.0 Hz), 8.04 (dd, 1 H, J = 7.8, 9.0 Hz), 7.74 (s, 1 H), 7.32 (d, 1 H, J = 7.8 Hz), 4.21 (s, 3 H), 3.34-3.42 (m, 1 H), 3.33 (s, 3 H), 3.12 (s, 3 H), 1.48 (d, 6 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 150.06, 145.47, 141.95, 140.49, 134.92, 107.92, 107.57, 106.10, 37.57, 37.48, 33.33, 24.71, 21.40. Anal. Calcd for $C_{14}H_{20}IN_3O_2 \cdot 1/2 H_2O$: C, 42.22; H, 5.32; N, 10.55. Found: C, 42.19; H, 5.36; N, 10.45.

2-Phenylimidazo[1,2-a]pyridin-5-ol (13b) A solution of 2-bromoacetophenone (19.9 g, 0.1 mol) in dry THF (60 mL) was added dropwise to a mixture of 2,6-diaminopyridine (10.9 g, 0.1 mol) in THF (80 mL) at reflux temperature. The mixture was stirred at reflux overnight. Additional 2,6-diaminopyridine (3g) was added to the mixture which was refluxed for a further 5 h. The solvent was evaporated to dryness and the resulting residue was washed with Et₂O (3 x 100 mL) and then dissolved in methanol (150 mL). Conc'd HBr solution (3 mL) was added and the mixture was stirred at reflux for 30 min. Solvent was evaporated to dryness. The residue was neutralized with sat'd NaHCO₃ solution and the mixture was extracted with CHCl₃ (4 x 100 mL). The organic layers were washed with brine, dried (anhydrous Na₂SO₄) and filtered via a column of silica gel, eluted with a mixture of 20% hexane in ethyl acetate to give 5-amino-2-phenylimidazo[1,2-a]pyridine (5.27 g, 25.2%): R_f = 0.44 (EtOAc-hexane, 4:1); ¹H NMR (CDCl₃) δ 7.94, (dd, 2 H, J = 1.4, 8.4 Hz), 7.64 (s, 1 H), 7.37-7.43 (m, 2 H), 7.29-7.34 (m, 1 H), 7.17 (d, 1 H, J = 8.8 Hz), 7.09 (dd, 1 H, J = 7.2, 8.8 Hz), 6.04 (dd, 1 H, J = 1.1, 7.2 Hz), 4.45 (br s, 2 H). The treatment of 5-amino-2-phenylimidazo[1,2-a]pyridine (2.83 g, 13.5 mmol) with an aqueous 70% H₂SO₄ solution as described for **10a** gave **13b** (2.62 g, 92.2 %) as an olive green solid: R_f = 0.68 (CHCl₃-MeOH, 9:1); ¹H NMR (DMSO-d₆) δ 8.24 (s, 1 H), 7.89 (d, 2 H, J = 7.8 Hz), 7.35-7.50 (m, 5 H), 6.24 (d, 1 H, J = 8.1 Hz), 5.72 (d, 1 H, J = 8.4 Hz).

2-Phenyl-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (13c) Carbamoylation of **13b** (2.6 g, 12.3 mmol) with sodium hydride (0.2 g, 8.6 mmol) and N,N-dimethylcarbamoyl chloride (0.79 mL, 8.6 mmol) in dry DMF (25 mL) as described earlier for **12c** afforded a crude product which was purified by column chromatography (silica gel; 2% of MeOH in CHCl₃) to give **13c** (0.67 g, 42 %) as a yellow solid from EtOAc/hexane: mp 152-153 °C; R_f = 0.57 (CHCl₃-MeOH, 24:1); ¹H NMR (CDCl₃) δ 7.98 (d, 2 H, J = 7.2 Hz), 7.78 (s, 1 H), 7.51 (d, 1 H, J = 9.0 Hz), 7.43 (dd, 2 H, J = 7.2, 7.8 Hz), 7.32 (m, 1 H), 7.22 (dd, 1 H, J = 7.5, 9.0 Hz), 6.65 (d, 1 H, J = 7.5 Hz), 3.24 (s, 3 H), 3.09 (s, 3 H); ¹³C NMR (CDCl₃) δ 151.68, 147.18, 145.85, 140.66, 133.63, 128.60, 128.00, 126.19, 125.17, 113.80, 103.55, 101.97, 37.16, 36.78. Anal. Calcd for C₁₆H₁₅N₃O₂: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.24; H, 5.40; N, 14.89.

1-Methyl-2-phenyl-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium

Iodide (13d) (PN-III-236, BN38874) Following the general procedure for Quaternization, the reaction of **13c** (0.78 g, 2.8 mmol) with an excess of methyl iodide in dry THF (5 mL) gave **13d** (0.92 g, 78.5 %) as white needles from (CH₃)₂CO/Et₂O: mp 156-157 °C; IR (KBr)_{vmax} 1755 cm⁻¹; ¹H NMR (CDCl₃) δ 8.16 (d, 1 H, J = 9.0 Hz), 8.04 (dd, 1 H, J = 8.0, 9.0 Hz), 7.96 (s, 1 H), 7.71-7.75 (m, 2 H), 7.57 - 7.62 (m, 3 H), 7.36 (dd, 1 H, J = 0.6, 8.0 Hz), 4.15 (s, 3 H), 3.29 (s, 3 H), 3.11 (s, 3 H); ¹³C NMR (CDCl₃) δ 150.22, 142.09, 140.90, 138.93, 135.35, 131.22, 130.29, 129.38, 124.28, 108.76, 108.16, 108.04, 37.58, 34.18. Anal. Calcd for: C₁₇H₁₈IN₃O₂: C, 48.24; H, 4.29; N, 9.93. Found: C, 48.08; H, 4.32; N, 9.93.

5-Hydroxy-2-(p-nitrophenylazo)pyridine. (7) To a solution of p-nitroaniline (7.4 g, 53.5 mmol) in hydrochloric acid (60 mL, 1 part of water and 1 part of conc HCl) was added an ice cold solution of sodium nitrite (5.5 g, 79.9 mmol) in water (12 mL). The addition was done at -5 °C. The diazonium chloride solution was then added to a cold solution of 3-hydroxypyridine (5.0 g, 52.5 mmol) and sodium hydroxide (2.1 g, 52.5 mmol) in water (100 mL) in such a way that the pH of the reaction mixture was maintained close to neutral. After stirring for an additional hour the mixture was acidified with glacial acetic acid, filtered and dried. The solid obtained was a mixture of two isomers and the mixture was used without crystallization for the next step.

5-Benzoyloxy-2-(p-nitrophenylazo)pyridine. To a solution of the above azo dye (mixture of isomers) (5.46 g, 22.3 mmol) and potassium carbonate (6.1 g, 44.0 mmol) in water (150 mL) was added benzoyl chloride (3.8 mL, 32.7 mmol) at rt. The mixture was stirred for 1 hour and the precipitate obtained was filtered, and washed thoroughly with water, dried and crystallized from benzene to give 5.2 g (67%) of the desired 5-benzoyloxy-2-(p-nitrophenylazo)pyridine.

2-Amino-5-benzoyloxypyridine (14) To a suspension of 5-benzoyloxy-2-(p-nitrophenylazo)pyridine (9.5 g, 27.2 mmol) and 10%-Pd/C (0.490 g) in ethanol (250 mL) was added a solution of sodium hypophosphite (20.7 g, 195 mmol) in water (125 mL). The reaction mixture was heated to reflux for 1.5 h and the combined filtrate

was cooled and neutralized with saturated sodium bicarbonate solution. The crystalline solid obtained was filtered and dried to give 4.5 g (77%) of the amine.

6-Benzoyloxyimidazo[1,2-a]pyridine (15a) A mixture of 2-amino-5-benzoyloxypyridine (6.52 g, 30.4 mmol) and chloroacetaldehyde (6.37 g, 36.5 mmol, 45% w/w in water) in acetone (150 mL) was gently refluxed. The reaction mixture was evaporated to dryness under aspirator pressure. The resulting residue was neutralized with sat'd NaHCO_3 solution and extracted with CHCl_3 (4 x 100 mL). The organic layers were washed with brine (2 x 100 mL), dried (anhydrous Na_2SO_4), filtered and evaporated to dryness. Purification of the crude by column chromatography (silica gel, 20% of hexane in EtOAc) gave **15a** (3.34 g, 46 %) as a tan solid from EtOAc/hexane: mp 144-145 °C; R_f = 0.25 (EtOAc-hexane, 5:1); ^1H NMR (CDCl_3) δ 8.28 (d, 1 H, J = 2.1 Hz), 8.19-8.22 (m, 2 H), 7.51-7.70 (m, 6 H), 7.12 (dd, 1 H, J = 2.1, 9.6 Hz); ^{13}C NMR (CDCl_3) δ 164.87, 154.77, 143.76, 139.69, 134.63, 134.02, 130.20, 128.69, 121.13, 118.54, 117.80, 113.40. Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.47; H, 4.22; N, 11.75.

6-(N,N-Dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (15b) A mixture of **15a** (1.80 g, 7.6 mmol) and sodium methoxide (0.61 g, 11.3 mmol) in dry pyridine (50 mL) was stirred at 75 °C overnight. N,N-dimethylcarbamoyl chloride (1.18 mL, 12.8 mmol) was added slowly via syringe. The reaction mixture was stirred for 10 h. Solvent was removed to dryness and the resulting residue was partitioned between a sat'd solution of NaHCO_3 and CHCl_3 . The aqueous phase was extracted with CHCl_3 (4 x 30 mL). The organic layers were washed with brine, dried (anhydrous Na_2SO_4) and filtered. Removal of solvent to dryness gave a crude which was purified by column chromatography (silica gel, CHCl_3 -MeOH, 50:1) to give **15b** (1.37g, 88.8%) as a pale yellow solid from EtOAc/hexane: mp 123-123.5 °C; R_f = 0.23 (CHCl_3 -MeOH, 50:1); ^1H NMR (CDCl_3) δ 8.13 (ca, 1 H), 7.63 (d, 1 H, J = 1.2 Hz), 7.57 (d, 1 H, J = 9.6 Hz), 7.55 (s, 1 H), 7.03 (dd, 1 H, J = 2.1, 9.6 Hz), 3.11 (s, 3 H), 3.03 (s, 3 H); ^{13}C NMR (CDCl_3) δ 143.67, 140.21, 134.36, 121.70, 118.48, 117.39, 113.19, 36.86, 36.47. Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.67; H, 5.52; N, 20.54.

1-Methyl-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium

***p*-Toluenesulfonate (15c) (PN-III-268, BN40481)** Following the general procedure for Quaternization, the reaction of **15b** (0.103 g, 0.5 mmol) with methyl *p*-toluenesulfonate (0.14 g, 0.75 mmol) in dry THF (5 mL) gave **15c** (0.19 g, 97 %) as a white solid: mp 176-177 °C; IR (KBr) ν_{max} 3138, 3045, 1732, 1184 cm^{-1} ; ^1H NMR (CDCl_3) δ 9.05 (d, 1 H, $J = 1.8$ Hz), 8.65 (d, 1 H, $J = 1.8$ Hz), 8.13 (d, 1 H, $J = 1.8$ Hz), 7.99 (d, 1 H, $J = 9.6$ Hz), 7.79 (d, 2 H, $J = 8.1$ Hz), 7.66 (dd, 1 H, $J = 1.8, 9.6$ Hz), 7.13 (d, 2 H, $J = 8.1$ Hz), 4.12 (s, 3 H), 3.09 (s, 3 H), 3.01 (s, 3 H), 2.33 (s, 3 H); ^{13}C NMR (CDCl_3) δ 153.23, 143.98, 143.22, 139.08, 136.96, 130.66, 128.55, 127.47, 125.81, 122.85, 116.10, 110.61, 36.94, 36.60, 34.60, 21.22. Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_5\text{S}$: C, 55.23; H, 5.41; N, 10.73. Found: C, 55.49; H, 5.40; N, 10.72.

2-Methyl-6-benzoyloxyimidazo[1,2-a]pyridine (16a) A mixture of 2-amino-5-benzoyloxypyridine (1.79 g, 8.36 mmol) and chloroacetone (0.77 mL, 9.2 mmol) in absolute ethanol (35 mL) was refluxed for 10 h. Two more portions of chloroacetone were added (0.3 mL each) over a period of 10 h. The solvent was then removed to dryness under reduced pressure. The resulting residue was treated with a sat d NaHCO_3 solution. The aqueous mixture was extracted with CHCl_3 (4 x 25 mL) and dried (anhydrous Na_2SO_4). Removal of solvent to dryness gave a crude, which was purified by column chromatography (silica gel, EtOAc-hexane, 2:1) to give **16a** (0.88 g, 41.8%) as off-white needles from EtOAc/hexane: mp 178-180 °C; $R_f = 0.25$ (EtOAc-hexane, 2:1); ^1H NMR (CDCl_3) δ 8.20 (ca, 1 H), 8.15-8.17 (m, 2 H), 7.62-7.68 (m, 1 H), 7.49-7.54 (m, 3 H), 7.34 (d, 1 H, $J = 0.3$ Hz), 7.05 (dd, 1 H, $J = 2.1, 9.6$ Hz), 2.46 (s, 3 H); ^{13}C NMR (CDCl_3) δ 164.87, 144.47, 143.26, 139.21, 133.88, 130.10, 128.60, 120.42, 117.95, 116.55, 110.51, 14.33. Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.25; H, 4.91; N, 11.22.

2-Methyl-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (16b) The reaction of **16a** (3.3 g, 13.1 mmol) with sodium methoxide (1.06 g, 19.6 mmol) and N,N-dimethylcarbamoyl chloride (2.4 mL, 26.2 mmol) in dry pyridine (25 mL) at 95 °C (oil bath temperature) as described for **15b** gave **16b** (0.89 g, 31%) after purification by column chromatography (silica gel, gradient elution, 2-14% of ethanol in EtOAc). Decolorization of **16b** with charcoal in MeOH followed by

recrystallization in EtOAc/hexane gave pale yellow needles: mp 133-134 °C; R_f = 0.40 (EtOAc-EtOH, 9:1); ^1H NMR (CDCl_3) δ 8.02 (d, 1 H, J = 2.1 Hz), 7.44 (d, 1 H, J = 9.6 Hz), 7.30 (s, 1 H), 6.97 (dd, 1 H, J = 2.1, 9.6 Hz), 3.10 (s, 3 H), 3.02 (s, 3 H), 2.44 (s, 3 H); ^{13}C NMR (CDCl_3) δ 154.40, 144.20, 143.22, 139.78, 121.04, 117.98, 116.22, 110.34, 36.80, 36.42, 14.37. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.33; H, 6.02; N, 19.15.

1,2-Dimethyl-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium

***p*-Toluenesulfonate (16c) (PN-IV-33, BN40507)** Following the general procedure for Quaternization, the treatment of **16b** (55 mg, 0.25 mmol) with methyl *p*-toluenesulfonate (70 mg, 0.37 mmol) in dry THF (2 mL) gave **16c** (95 mg, 94 %) as a white solid from MeOH/Et₂O: mp 223-224 °C; IR (KBr) $_{\text{vmax}}$ 3113, 3049, 1716, 1184 cm^{-1} ; ^1H NMR (DMSO-d_6) δ 8.97 (d, 1 H, J = 1.9 Hz), 8.18 (d, 1 H, J = 9.8 Hz), 8.15 (s, 1 H), 7.92 (dd, 1 H, J = 1.9, 9.8 Hz), 7.46 (d, 2 H, J = 7.9 Hz), 7.08 (d, 2 H, J = 7.9 Hz), 3.90 (s, 3 H), 3.08 (s, 3 H), 2.95 (s, 3 H), 2.49 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 152.93, 145.85, 142.44, 137.28, 137.10, 135.84, 129.37, 127.79, 125.32, 121.56, 112.42, 110.68, 36.43, 36.09, 30.79, 20.59, 9.22. Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_5\text{S}$: C, 56.28; H, 5.72; N, 10.36. Found: C, 56.37; H, 5.78; N, 10.36.

2-(2-Propyl)imidazo[1,2-a]pyridin-6-ol (17a) A mixture of 2-amino-5-benzoyloxypyridine (0.89 g, 4.2 mmol) and 1-bromo-3-methylbutan-2-one (**6**) (0.75g, 4.6 mmol) in dry THF (15 mL) was refluxed for 16 h. Solvent was removed to dryness and the resulting residue was treated with aqueous 20% KOH solution. The mixture was stirred at 100 °C (oil bath temperature) for 1 h, then cooled and neutralized with Conc HCl solution to give solid **17a** (0.52 g, 71 %): R_f = 0.43 (CHCl_3 -MeOH, 9:1); ^1H NMR (CDCl_3) δ 7.76 (d, 1 H, J = 1.8 Hz), 7.19 (overlapped d, 1 H, J = 9.6 Hz), 7.18 (overlapped s, 1 H), 7.02 (dd, 1 H, J = 1.8, 9.6 Hz), 3.08 (septet, 1 H, J = 7.1 Hz), 1.32 (d, 6 H, J = 7.1 Hz); ^{13}C NMR (CDCl_3) δ 151.97, 147.48, 140.81, 121.46, 115.01, 110.72, 107.87, 27.92, 22.46.

2-(2-Propyl)-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (17b) A mixture of **17a** (0.21 g, 1.2 mmol) and N,N-dimethylcarbamoyl chloride (0.19 g, 1.8 mmol) in dry pyridine (10 mL) was stirred at 80 °C overnight. Solvent was then

evaporated to dryness under reduced pressure and the resulting residue was partitioned between a saturated NaHCO_3 solution and CHCl_3 . The aqueous phase was extracted with CHCl_3 (6 x 20 mL). The organic layers were washed with brine (2 x 20 mL), dried (anhydrous Na_2SO_4), filtered and evaporated to dryness. Purification of the crude by column chromatography (silica gel; EtOAc-hexane, 4:1) afforded **17b** (0.21 g, 70%) as a thick oil: $R_f = 0.29$ (EtOAc-hexane, 4:1); ^1H NMR (CDCl_3) δ 7.95 (d, 1 H, $J = 2.2$ Hz), 7.39 (d, 1 H, $J = 9.9$ Hz), 7.20 (s, 1 H), 6.87 (dd, 1 H, $J = 2.2, 9.9$ Hz), 2.92-3.07 (overlapped m, 4 H), 2.91 (s, 3 H), 1.26 (d, 6 H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3) δ 154.75, 154.20, 142.90, 139.51, 120.89, 118.06, 116.19, 108.15, 36.50, 36.19, 28.21, 22.20.

1-Methyl-2-(2-propyl)-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Iodide (17c) (PN-III-240, BN38883) Following the general procedure for Quaternization, **17b** (1.27 g, 5.1 mmol) was reacted with an excess of methyl iodide in dry THF to give **17c** (1.65 g, 82.5 %) as an off-white solid from $\text{CH}_3\text{CN}/\text{Et}_2\text{O}$: mp 180-181 °C; IR (KBr) ν_{max} 3068, 3032, 1734 cm^{-1} ; ^1H NMR (CDCl_3) δ 9.10 (d, 1 H, $J = 2.1$ Hz), 8.58 (s, 1 H), 8.28 (d, 1 H, $J = 9.9$ Hz), 7.77 (dd, 1 H, $J = 2.1, 9.9$ Hz), 4.15 (s, 3 H), 3.28 (septet, 1 H, $J = 6.9$ Hz), 3.14 (s, 3 H), 3.02 (s, 3 H), 1.43 (d, 6 H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3) δ 153.11, 145.49, 143.40, 137.49, 130.52, 121.77, 112.09, 111.40, 37.10, 36.84, 33.04, 24.96, 21.55. Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{IN}_3\text{O}_2$: C, 43.20; H, 5.18; N, 10.80. Found: C, 43.04; H, 5.23; N, 10.79.

2-Amino-4-(N,N-dimethylcarbamoyloxy)pyridine (19) To a suspension of NaH (2.10 g, 52.5 mmol) (washed with hexane) in dry THF (100 mL), was added portionwise powdery 2-amino-4-hydroxypyridine (5.50 g, 50 mmol). The mixture was refluxed for 17.5 h. N,N-Dimethylcarbamoyl chloride (5.0 mL, 53 mmol) was then added dropwise. The mixture was refluxed further for 30 h. After cooling, the mixture was filtered and washed with THF. The filtration was evaporated to dryness to afford **19** as a yellow solid (7.75 g, 85 %). Purification by flash column chromatography (silica gel, acetone:MeOH: CH_2Cl_2 =10:1:40) followed by recrystallization from acetone/ether gave a white solid: mp 104-5 °C; IR (KBr) ν_{max} 3420, 3311, 3161, 2942, 1724, 1647, 1602, 1566, 1485, 1448, 1392, 1346, 1306, 1267, 1175, 953, 847, 799, 747 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.99 (d, $J = 6.0$

Hz, 1H), 6.50 (dd, $J = 2.1, 6.0$ Hz, 1H), 6.41 (d, $J = 2.1$ Hz, 1H), 4.70 (br s, 2H), 3.08 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 160.62, 160.36, 153.85, 149.82, 108.19, 101.07, 37.18, 36.99; MS (CI, methane) m/z 182 ($M+1$, 100). Anal. Calcd for $\text{C}_8\text{H}_{11}\text{N}_3\text{O}_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.07; H, 6.10; N, 23.08.

7-(N,N-Dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (20a) A mixture of α -chloroacetylaldehyde (3.14 g, 18 mmol) and 2-amino-4-(N,N-dimethylcarbamoyloxy)pyridine (2.72 g, 15 mmol) were refluxed in THF for 13 h. The solvent was removed under reduced pressure. The residue was taken up by CH_2Cl_2 (100 mL) and washed with sat d NaHCO_3 (2x10mL) and brine (10 mL). The aqueous washings were combined and extracted with CH_2Cl_2 (4x20 mL). The CH_2Cl_2 were combined and dried over anhydrous MgSO_4 , and CH_2Cl_2 was evaporated. The residue was purified by flash column chromatography (silica gel, 5% to 10% MeOH in CH_2Cl_2) to afford **20a** (2.122 g, 69%) as a white solid from ether: mp 98-100 °C; IR (KBr) ν_{max} 3433, 3117, 3052, 2942, 1721, 1645, 1532, 1508, 1472, 1441, 1389, 1316, 1277, 1235, 1182, 1151, 1121, 1078, 1011, 910, 858, 829, 808, 735 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.07 (d, $J = 7.2$ Hz, 1H), 7.61 (s, 1H), 7.54 (s, 1H), 7.35 (d, $J = 2.4$ Hz, 1H), 6.73 (dd, $J = 2.4, 7.2$ Hz, 1H), 3.12 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.49, 149.13, 146.11, 134.70, 126.28, 112.53, 110.22, 108.81, 37.27, 37.02; MS (EI) m/z 206 ($M+1$, 8.9), 205 (M , 31.6). Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.62; H, 5.40; N, 20.39.

2-Methyl-7-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (21a) A mixture of α -chloroacetone (4 mL, 50.0 mmol), 2-amino-4-(N,N-dimethylcarbamoyloxy)pyridine (1.81 g, 10.0 mmol) and toluensulfonic acid (57 mg, 0.30 mmol) in benzene (30 mL) were refluxed in a round bottom flask (100 mL) equipped with Dean-Stock distillation apparatus. After 9 h, additional α -chloroacetone (4 mL, 50.0 mmol) was added, and the reaction was refluxed further for 17 h. The benzene was removed under reduced pressure. The residue was taken up by CH_2Cl_2 (100 mL) and washed with sat d NaHCO_3 (2x10 mL) and brine (10 mL). The aqueous washings were combined and extracted with CH_2Cl_2 (4x20 mL). The CH_2Cl_2 were combined and dried over anhydrous MgSO_4 , and CH_2Cl_2 was evaporated. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2 :EtOAc:MeOH =

50:50:1) to afford **21a** (0.752 g, 34 %) as white crystals from ether: mp 95-6 °C; IR (KBr) ν_{max} 3043, 2931, 1726, 1643, 1528, 1508, 1476, 1445, 1385, 1327, 1275, 1246, 1173, 1015, 855, 754, 719 cm^{-1} ; ^1H NMR (300 MHz, acetone- d_6) δ 8.31 (d, J = 7.2 Hz, 1H), 7.53 (s, 1H), 7.14 (d, J = 1.8 Hz, 1H), 6.67 (dd, J = 1.8, 7.2 Hz, 1H), 3.10 (s, 3H), 2.96 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.56, 148.88, 145.72, 144.54, 125.68, 109.53, 109.46, 107.90, 37.24, 36.99, 14.81; MS (CI, methane) m/z 220 ($M+1$, 100). Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.37; H, 5.99; N, 19.14.

2-Isopropyl-7-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (22a) A mixture of 1-bromo-3-methylbutan-2-one (**6**) (1.98 g, 12.0 mmol), 2-amino-4-(N,N-dimethylcarbamoyloxy)pyridine (1.81 g, 10.0 mmol) and toluenesulfonic acid (57 mg, 0.30 mmol) in toluene (30 mL) was refluxed for 24 h. The toluene was removed under reduced pressure. The residue was taken up by CH_2Cl_2 (100 mL) and washed with sat d NaHCO_3 (2x10 mL) and brine (10 mL). The aqueous washings were combined and extracted with CH_2Cl_2 (5x20 mL). The CH_2Cl_2 were combined and dried over anhydrous MgSO_4 , and CH_2Cl_2 was evaporated. The residue was purified by flash column chromatography (silica gel, 20% acetone in CH_2Cl_2) to afford **22a** (1.516 g, 61 %) as white needle crystals from ether: mp 106-7 °C; IR (KBr) ν_{max} 3144, 3080, 2953, 2868, 1719, 1640, 1526, 1505, 1470, 1437, 1393, 1287, 1238, 1181, 1015, 868, 799, 789, 737 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.97 (d, J = 7.2 Hz, 1H), 7.27 (s, 1H), 7.25 (d, J = 2.4 Hz, 1H), 6.64 (dd, J = 2.4, 7.2 Hz, 1H), 3.11 (s, 3H), 3.09 (m, 1H), 3.02 (s, 3H), 1.35 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.40, 154.54, 148.87, 145.60, 125.94, 109.41, 108.12, 107.47, 37.21, 36.98, 28.89, 22.87; MS (CI, methane) m/z 248 ($M+1$, 100). Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.22; H, 6.99; N, 16.97.

2-Phenyl-7-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (23a) A mixture of α -bromoacetophenone (1.99 g, 10.0 mmol), 2-amino-4-(N,N-dimethylcarbamoyloxy)pyridine (1.81 g, 10.0 mmol) and toluenesulfonic acid (57 mg, 0.30 mmol) were refluxed in toluene for 22 h. The toluene was removed under reduced pressure. The residue was taken up by CH_2Cl_2 (100 mL) and washed with sat d NaHCO_3 (2x10mL) and brine (10 mL). The aqueous washings were combined

and extracted with CH_2Cl_2 (4x20 mL). The CH_2Cl_2 were combined and dried over anhydrous MgSO_4 , and CH_2Cl_2 was evaporated. The residue was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to afford **23a** (1.524 g, 54 %) as white needle crystals from acetone: mp 184-5 °C; IR (KBr) ν_{max} 3136, 3084, 2942, 1725, 1642, 1526, 1505, 1472, 1443, 1391, 1370, 1254, 1204, 1184, 1169, 1074, 1009, 872, 787, 775, 719, 694 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.06 (dd, J = 0.9, 7.2 Hz, 1H), 7.94 (m, 2H), 7.82 (s, 1H), 7.46-7.28 (m, 4H), 6.73 (dd, J = 2.4, 7.2 Hz, 1H), 3.13 (s, 3H), 3.04 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.46, 149.39, 147.06, 146.43, 134.22, 129.20, 128.45, 126.53, 126.09, 110.27, 108.52, 108.27, 37.31, 37.06; MS (EI) m/z 282 ($M+1$, 4.8), 205 (M , 30.0), 209 ($M-\text{Me}_2\text{NCO}$, 4.5), 72 (Me_2NCO , 100). Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.41; H, 5.41; N, 14.98.

General Procedure for Quaternization of 7-(N,N-dimethylcarbamoyloxy)-imidazo[1,2-a]pyridine derivatives A mixture of appropriate carbamate (1 equiv) and methyl iodide (1.5-10 equiv) in dry THF was stirred at 50 °C (oil bath) for 12-43 hours. The mixture was cooled to rt and filtered. The product was washed with dry THF and dried *in vacuo* at rt.

1-Methyl-7-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Iodide (20b) (SJ-II-43) Following the general procedure for Quaternization, **20a** (0.584 g, 2.84 mmol) was reacted with an excess of methyl iodide (0.27 mL, 4.27 mmol) in dry THF (5 mL) for 12 h to give **20b** (0.920 g, 93%) as a light yellow solid from MeOH/ Et_2O : mp 147-8 °C; IR (KBr) ν_{max} 3071, 3034, 1740, 1655, 1547, 1456, 1377, 1271, 1260, 1200, 1144, 1099, 1007, 841, 808, 773, 729, 638 cm^{-1} ; ^1H NMR (300 MHz, acetone- d_6) δ 9.21 (d, J = 7.5 Hz, 1H), 8.59 (d, J = 1.8 Hz, 1H), 8.25 (d, J = 1.8 Hz, 1H), 8.08 (d, J = 2.1 Hz, 1H), 7.51 (dd, J = 2.1, 7.5 Hz, 1H), 4.22 (s, 3H), 3.16 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 156.18, 152.48, 140.91, 131.44, 127.38, 115.36, 114.21, 101.67, 37.61, 37.54, 35.85. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_3\text{O}_2\text{I}$: C, 38.06; H, 4.06; N, 12.10; I, 36.56. Found: C, 38.16; H, 4.03; N, 12.15; I, 36.65.

1-Methyl-2-methyl-7-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Iodide (21b) (SJ-II-100) Following the general procedure for Quaternization, **21a**

(1.417 g, 6.47 mmol) was reacted with an excess of methyl iodide (2.01 mL, 30.85 mmol) in dry THF (10 mL) for 24 h to give **21b** (2.20 g, 94%) as a off-white solid from MeOH/Et₂O: mp 216-8 °C; IR (KBr) ν_{max} 2978, 1734, 1659, 1549, 1499, 1476, 1433, 1399, 1381, 1256, 1209, 1198, 1146, 1007, 893, 800, 725 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.25 (d, J = 7.2 Hz, 1H), 8.50 (s, 1H), 7.83 (s, 1H), 7.19 (dd, J = 2.1, 7.5 Hz, 1H), 3.93 (s, 3H), 3.11 (s, 3H), 2.99 (s, 3H), 2.52 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.79, 152.59, 141.00, 135.55, 130.90, 113.86, 112.98, 101.66, 37.58, 37.51, 32.80, 11.23. Anal. Calcd for C₁₂H₁₆N₃O₂I: C, 39.91; H, 4.47; N, 11.63, I, 35.14. Found: C, 40.00; H, 4.43; N, 11.56; I, 35.06.

1-Methyl-2-isopropyl-7-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium

Iodide (22b) (SJ-II-95) Following the general procedure for Quaternization, **22a** (1.05 g, 4.25 mmol) was reacted with an excess of methyl iodide (1.32 mL, 21.25 mmol) in dry THF (25 mL) for 24 h to give **22b** (1.56g, 94%) as a off-white solid from MeOH/Et₂O: mp 196-7 °C; (KBr) ν_{max} 3049, 3023, 2972, 1746, 1657, 1547, 1534, 1464, 1379, 1252, 1198, 1150, 1007, 847, 808, 783, 748 cm⁻¹; ¹H NMR (300 MHz, acetone-d₆) δ 9.02 (dd, J = 0.6, 7.2 Hz, 1H), 8.35 (s, 1H), 8.05 (d, J = 2.4 Hz, 1H), 7.48 (dd, J = 2.4, 7.2 Hz, 1H), 4.13 (s, 3H), 3.42 (m, 1H), 3.15 (s, 3H), 3.02 (s, 3H), 1.44 (d, J = 6.6 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 155.94, 152.56, 145.39, 141.19, 131.22, 113.92, 111.61, 101.72, 37.56, 37.50, 32.91, 25.24, 21.96. Anal. Calcd for C₁₄H₂₀N₃O₂I: C, 43.20; H, 5.18; N, 10.80, I, 32.60. Found: C, 43.28; H, 5.17; N, 10.83; I, 32.50.

1-Methyl-2-phenyl-7-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium

Iodide (23b) (SJ-II-39) Following the general procedure for Quaternization, **23a** (1.554 g, 5.524 mmol) was reacted with an excess of methyl iodide (1.72 mL, 27.6 mmol) in dry THF (25 mL) for 24 h. Another portion of methyl iodide (1.72 mL, 27.6 mmol) was added, and the reaction was stirred further for 19 h to give **23b** (2.134 g, 91%) as a light yellow solid from MeOH/Et₂O: mp 212-4 °C; IR (KBr) ν_{max} 3142, 2996, 2934, 1736, 1659, 1537, 1489, 1443, 1387, 1265, 1204, 1157, 1017, 891, 810, 779, 758, 748, 727, 702 cm⁻¹; ¹H NMR (300 MHz, acetone-d₆) δ 9.28 (d, J = 7.2 Hz, 1H), 8.77 (s, 1H), 8.15 (d, J = 1.8 Hz, 1H), 7.80-7.72 (m, 2H), 7.68-7.63 (m, 3H), 7.55 (dd, J = 1.8, 7.2 Hz, 1H), 4.09 (s, 3H), 3.18 (s, 3H), 3.04 (s, 3H); ¹³C NMR (75

MHz, CDCl_3) δ 156.22, 152.52, 141.53, 138.79, 131.51, 131.39, 130.44, 129.94, 125.08, 114.18, 113.24, 102.08, 37.57, 37.50, 33.64. Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}_2\text{I}$: C, 48.24; H, 4.29; N, 9.93; I, 29.98. Found: C, 48.15; H, 4.29; N, 9.84; I, 30.02.

General Procedure for Carbamoylation of 8-Hydroxyimidazo[1,2-a]pyridine Derivatives

A mixture of 8-hydroxyimidazo[1,2-a]pyridine derivative (1 equiv) and N,N-dimethylcarbamoyl chloride (1.5 equiv) in pyridine was stirred at 80 °C for 16 h. Solvent was evaporated under reduced pressure to dryness and the resulting residue was neutralized with saturated NaHCO_3 solution. The aqueous mixture was extracted with CHCl_3 (6x). The organic layers were washed with water, brine and dried (Na_2SO_4). Removal of solvent gave a crude product.

8-(N,N-Dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (25b) Following the general procedure for carbamoylation, the reaction of 8-hydroxyimidazo[1,2-a]pyridine (9) **25a** (8.5 g, 5.0 mmol) with N,N-dimethylcarbamoyl chloride (0.69 mL, 7.5 mmol) in pyridine (5 mL) gave **25b** (0.67 g, 65%) as a white solid after purification by column chromatography (silica gel; CHCl_3 -MeOH, 25:1) followed by recrystallization in EtOAc/hexane: mp 128-129.5 °C; R_f = 0.29 (CHCl_3 -MeOH, 25:1); ^1H NMR (CDCl_3) δ 7.86 (br d, 1 H, J = 6.9 Hz), 7.48 (br d, 2H, J = 8.7 Hz), 6.86 (br d, 1 H, J = 7.4 Hz), 6.57 (dd, 1 H, J = 6.9, 7.4 Hz), 3.12 (s, 3 H), 2.94 (s, 3 H). ^{13}C NMR (CDCl_3) δ 153.70, 140.95, 140.72, 133.46, 123.06, 115.35, 113.19, 111.42, 36.80, 36.67. Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_2$: C, 58.53; H, 5.40 N, 20.48. Found: C, 58.46 H, 5.46; N, 20.53.

1-Methyl-8-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium

***p*-Toluenesulfonate (25c) (PN-II-278, BN36049)** Following the general procedure for Quaternization, the reaction of **25b** (0.96 g, 4.68 mmol) with methyl *p*-toluenesulfonate (1.3 g, 7.0 mmol) in THF (20 mL) gave **25c** (1.38 g, 75%) as white solid from $\text{CH}_3\text{CN}/\text{Et}_2\text{O}$: mp 145-145.5 °C; IR (KBr) $_{\text{vmax}}$ 3107, 3086, 1751, 1199 cm^{-1} ; ^1H NMR (CDCl_3) δ 9.12 (d, 1 H, J = 6.8 Hz), 8.79 (d, 1 H, J = 2.1 Hz), 8.33 (d, 1 H, J = 2.1 Hz), 7.78 (d, 2 H, J = 8.0 Hz), 7.51 (d, 1 H, J = 7.8 Hz), 7.25 (dd, 1 H, J = 6.8, 7.8 Hz), 7.12 (d, 2 H, J = 8.0 Hz), 4.20 (s, 3 H), 3.15 (s, 3 H), 3.04 (s, 3 H), 2.13 (s, 3 H); ^{13}C NMR (CDCl_3) δ 152.72, 144.07, 139.13, 136.66, 134.17, 128.61,

128.49, 128.11, 125.86, 116.85, 116.42, 37.34, 36.79, 36.66, 21.27. Anal. Calcd for $C_{18}H_{21}N_3O_5S$: C, 55.23; H, 5.41; N, 10.73. Found: C, 55.29; H, 5.40; N, 10.72.

2-Methyl-8-hydroxyimidazo[1,2-a]pyridine (26a) A mixture of 2-amino-3-hydroxypyridine (1.10 g, 10 mmol) and 2-chloroacetone (0.8 mL, 10 mmol) in dry THF (30 mL) was gently refluxed for 5 h. Then another 0.8 mL of 2-chloroacetone was added and the reaction mixture was stirred at reflux temperature overnight. Solvent was then evaporated to dryness and the resulting residue was quenched with a saturated aqueous solution of $NaHCO_3$. The mixture was filtered to yield **26a** (0.52 g, 35%) as a tan solid. The aqueous filtrate was extracted with $CHCl_3$ (4 x 10 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of solvent gave another 0.26 g (18%) of **26a**: 1H NMR (D_2O) δ 7.96 (dd, 1 H, $J = 1.2, 6.3$ Hz); 7.61 (d, 1 H, $J = 0.9$ Hz), 7.06 (dd, 1 H, $J = 6.3, 7.8$ Hz), 7.01 (dd, 1 H, $J = 1.2, 7.8$ Hz), 2.38 (d, 3 H, $J = 0.9$ Hz); ^{13}C NMR ($DMSO-d_6$) δ 142.60, 133.31, 132.90, 119.29, 117.35, 112.81, 112.43, 10.21.

2-Methyl-8-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (26b) Following the general procedure for carbamoylation of 8-hydroxyimidazo[1,2-a]pyridine derivatives, **26a** (0.74 g, 5 mmol) and N,N-dimethylcarbamoyl chloride in dry pyridine yielded **26b** (0.8 g, 74%) as an off-white solid from EtOAc/hexane: mp 80.5-81.5 $^{\circ}C$; $R_f = 0.41$ ($CHCl_3$ -MeOH, 19:1); 1H NMR ($CDCl_3$) δ 7.88 (dd, 1 H, $J = 0.9, 6.8$ Hz), 7.35 (s, 1 H), 6.92 (dd, 1 H, $J = 0.9, 7.5$ Hz), 6.67 (dd, 1 H, $J = 6.8, 7.5$ Hz), 3.21 (s, 3 H), 3.03 (s, 3 H), 2.46 (d, 3 H, $J = 0.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 153.91, 143.46, 140.60, 139.87, 122.46, 115.20, 110.84, 110.52, 36.83, 36.78, 14.50. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.19; H, 6.01; N, 19.21.

1,2-Dimethyl-8-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Tosylate (26c) (PN-II-222, BN34830) Following the general procedure for Quaternization, the reaction of **26b** (0.4 g, 1.82 mmol) and methyl *p*-toluenesulfonate (0.5 g, 2.7 mmol) in THF (5 mL) afforded **26c** (0.52 g, 70%) as an off-white solid from methanol/ether: mp 205-207 $^{\circ}C$; IR (KBr) $_{\nu_{max}}$ 3136, 3049, 1728 cm^{-1} ; 1H NMR ($CDCl_3$) δ 9.06 (dd, 1 H, $J = 0.6, 6.6$ Hz), 8.57 (s, 1 H), 7.73 (d, 2 H, $J = 8.1$ Hz),

7.47 (dd, 1 H, $J = 0.6, 7.8$ Hz), 7.21 (dd, 1 H, $J = 6.6, 7.8$ Hz), 7.06 (dd, 2 H, $J = 8.1$ Hz), 3.99 (s, 3 H), 3.18 (s, 3 H), 3.04 (s, 3 H), 2.44 (s, 3 H), 2.28 (s, 3 H); ^{13}C NMR (CDCl_3) δ 152.67, 144.23, 138.72, 136.02, 135.62, 134.18, 128.31, 127.42, 125.74, 125.55, 116.43, 114.34, 37.21, 36.78, 32.77, 21.13, 9.92. Anal. Calcd for: $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_5\text{S}$: C, 56.28; H, 5.72; N, 10.36. Found: C, 56.25; H, 5.73; N, 10.31.

8-Hydroxy-2-(2-propyl)imidazo[1,2-a]pyridine (27a) To a hot solution of 2-amino-3-hydroxypyridine (3.3 g, 30 mmol) in absolute ethanol (30 mL) and THF (30 mL) was added dropwise a solution of 1-bromo-3-methylbutan-2-one (6) (4.95 g, 30 mmol). The reaction mixture was gently refluxed overnight and solvent was removed under reduced pressure. The residue was dissolved in methanol and a few drops of Conc. HBr were added. The mixture was heated on a steam bath for 1 h. Removal of solvent to dryness gave a brown solid, which was quenched with saturated NaHCO_3 solution. The mixture was extracted with CHCl_3 (6 x 30 mL). The organic layers were washed with H_2O (30 mL), brine (2 x 30 mL) and dried (Na_2SO_4). Evaporation of solvent gave a crude product. Purification of the crude by column chromatography on silica gel (CHCl_3 -MeOH, 19:1) afforded **27a** (3.9 g, 74%) as white solid from MeOH/ Et_2O : mp 162-163 °C; $R_f = 0.35$ (CHCl_3 -MeOH, 19:1); ^1H NMR (CDCl_3) δ 7.6 (dd, 1 H, $J = 4.5$ Hz), 7.23 (d, 1 H, $J = 0.6$ Hz), 6.66-6.71 (m, 2 H), 3.09-3.22 (m, 1 H), 1.28 (d, 6 H, $J = 6.9$ Hz), 0.47 (br s, 1 H); ^{13}C NMR (CDCl_3) δ 151.06, 146.98, 140.18, 116.54, 113.99, 108.28, 108.07, 27.62, 22.39. Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.11; H, 6.90; N, 15.83.

8-(N,N-Dimethylcarbamoyloxy)-2-(2-propyl)imidazo[1,2-a]pyridine (27b) Following the general procedure for carbamoylation of 8-hydroxyimidazo[1,2-a]pyridine derivatives, the reaction of **27a** (2.7 g, 15.3 mmol) with N,N-dimethylcarbamoyl chloride (2.1 mL, 23.0 mmol) in pyridine (30 mL) gave a crude product, which was purified by column chromatography (silica gel; EtOAc-hexane, 4:1) to give **27b** (2.71 g, 71 %) as a white solid from EtOAc/hexane: mp 100-101 °C; $R_f = 0.33$ (EtOAc-hexane, 4:1); ^1H NMR (CDCl_3) δ 7.90 (dd, 1 H, $J = 0.9, 6.9$ Hz), 7.35 (s, 1 H), 6.91 (dd, 1 H, $J = 0.9, 7.5$ Hz), 6.65 (dd, 1 H, $J = 6.9, 7.5$ Hz), 3.22 (s, 3 H), 3.08-3.20 (m, 1 H), 3.02 (s, 3 H), 1.34 (d, 6 H, $J = 6.9$ Hz). Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.01; H, 6.92; N, 16.98.

1-Methyl-2-(2-propyl)-8-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]-pyridinium *p*-Toluenesulfonate (27c) (PN-III-28, BN36058) Following the general procedure for Quaternization, the reaction of **27b** (1.1 g, 4.45 mmol) with methyl *p*-toluenesulfonate (1.24 g, 6.67 mmol) in CH₃CN (20 mL) gave **27c** (1.72 g, 89 %) as white solid from CH₃CN/Et₂O: mp 125-126 °C; IR (KBr)_{vmax} 3099, 3040, 1734, 1720, 1219 cm⁻¹; ¹H NMR (CDCl₃) δ 9.19 (d, 1 H, J = 6.7 Hz), 8.63 (s, 1 H), 7.76 (d, 2 H, J = 7.9 Hz), 7.48 (d, 1 H, J = 7.8 Hz), 7.22 (dd, 1 H, J = 6.7; 7.8 Hz), 7.06 (d, 2 H, J = 7.9 Hz), 4.03 (s, 3 H), 3.20 (s, 3 H), 3.08-3.18 (m, 1 H), 3.05 (s, 3 H), 2.28 (s, 3 H), 1.31 (d, 6 H, J = 6.9 Hz); ¹³C NMR (CDCl₃) δ 152.73, 145.16, 144.34, 138.61, 136.02, 134.37, 128.24, 128.06, 125.83, 125.79, 116.44, 113.05, 37.23, 36.00, 32.78, 24.22, 21.17, 21.11. Anal. Calcd for C₂₁H₂₇N₃O₅S: C, 58.18; H, 6.28; N, 9.69. Found: C, 57.98; H, 6.33; N, 9.58.

8-Hydroxy-2-phenylimidazo[1,2-a]pyridine (28a) A mixture of 2-amino-3-hydroxypyridine (1.10 g, 10 mmol) and 2-bromoacetophenone (1.99 g, 10 mmol) in acetone (30 mL) was stirred at 60 °C overnight. The volume of solvent was reduced and the mixture was cooled in an ice bath. The resulting solid was filtered, then dissolved in methanol, followed by addition of a few drops of Conc. HBr solution. The mixture was heated on a steam bath for 1 h. Solvent was evaporated to dryness. The residue was quenched with saturated NaHCO₃ solution. The aqueous mixture was extracted with CHCl₃ (6 x 20 mL). The organic layers were washed with brine (2 x 20 mL) and dried (Na₂SO₄). Removal of solvent gave **28a** (1.38 g, 66%) as a solid: R_f = 0.56 (CHCl₃-MeOH, 9:1); ¹H NMR (DMSO-d₆) δ 8.75 (s, 1 H), 8.35 (d, 1 H, J = 6.6 Hz), 8.00 (d, 2 H, J = 7.6 Hz), 7.51-7.60 (m, 3 H), 7.28 (dd, 1 H, J = 6.6, 7.5 Hz), 7.16 (d, 1 H, J = 7.8 Hz).

8-(N,N-Dimethylcarbamoyloxy)-2-phenylimidazo[1,2-a] pyridine (28b) Following the general procedure for carbamoylation of 8-hydroxyimidazo[1,2-a]-pyridine derivatives, treatment of **28a** (1.1 g, 5.2 mmol) with N,N-dimethylcarbamoyl chloride (0.72 mL, 7.8 mmol) in pyridine (10 mL) gave a crude product. Purification of the crude by column chromatography (silica gel; CHCl₃-MeOH, 20:1) afforded **28b** (1.2 g, 82%) as an off-white solid: mp 132-132.5 °C; R_f = 0.58 (CHCl₃-MeOH,

20:1); ^1H NMR (CDCl_3) δ 7.93 (dd, 1 H, $J = 1.5, 8.7$ Hz), 7.89 (dd, 1 H, $J = 1.0, 6.8$ Hz), 7.81 (s, 1 H), 7.37-7.41 (m, 2 H), 7.25-7.32 (m, 1 H), 6.96 (dd, 1 H, $J = 1.0, 7.5$ Hz), 6.63 (dd, 1 H, $J = 6.8, 7.5$ Hz), 3.24 (s, 3 H), 3.04 (s, 3 H); ^{13}C NMR (CDCl_3) δ 153.88, 145.66, 141.03, 140.41, 133.63, 128.42, 127.74, 126.16, 122.78, 115.48, 111.38, 109.06, 36.77. Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.41; H, 5.44; N, 14.92.

1-Methyl-2-phenyl-8-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium

Iodide (28c) (PN-II-258, BN36030) Following the general procedure for Quaternization, the reaction of **28b** (2.0g, 7.1 mmol) with methyl iodide (1.32 mL, 21.3 mmol) in THF (25 mL) yielded **28c** (2.47 g, 82%) as white needles from $\text{CH}_3\text{CN}/\text{Et}_2\text{O}$: mp 165-165.5 $^\circ\text{C}$; IR (KBr) $_{\text{vmax}}$ 3057, 1741, 1143 cm^{-1} ; ^1H NMR (CDCl_3) δ 9.38 (d, 1 H, $J = 6.7$ Hz), 8.95 (s, 1 H), 7.68 (d, 1 H, $J = 7.8$ Hz), 7.52-7.62 (m, 5 H), 7.36 (dd, 1 H, $J = 6.7, 7.8$ Hz), 4.00 (s, 3 H), 3.27 (s, 3 H), 3.09 (s, 3 H); ^{13}C NMR (CDCl_3) δ 152.60, 138.73, 136.75, 134.86, 131.05, 130.15, 129.30, 126.92, 126.44, 123.96, 117.07, 113.88, 37.34, 37.19, 34.63. Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}_2$: C, 48.24; H, 4.29; N, 9.93. Found: C, 48.34; H, 4.25; N, 9.97.

3-(N,N-dimethylcarbamoyloxy)pyridine (29a) Sodium hydride (3.3 g, 0.11 mol, 80% dispersion in mineral oil) was added in small portions to an ice-cooled solution of 3-pyridinol (9.51 g, 0.1 mol) in DMF (70 mL). The mixture was stirred in an ice bath for 10 min, then at room temperature for 30 min. The mixture was cooled and N,N-dimethylcarbamoyl chloride (0.13 mol, 11.96 mL) was added via syringe. The reaction mixture was then stirred at 80 $^\circ\text{C}$ for 2 h, cooled and poured into cold aqueous 1% KOH solution. The mixture was saturated with NaCl then extracted with benzene:petroleum ether (4:1) (3 x 80 mL). The combined organic layers were washed with H_2O (150 mL), then extracted with 5% HCl solution (3 x 75 mL). The cooled aqueous phase was basified with 20% KOH solution and extracted with benzene:petroleum ether (4:1) (3 x 80 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of solvent gave a pale yellow liquid **29a** (11.05 g, 66.4%): ^1H NMR (CDCl_3) δ 8.43-8.45 (br s, 1 H), 7.51 (ddd, 1 H, $J = 1.3$ Hz, $J = 2.5$ Hz, $J = 8.3$ Hz), 7.30 (dd, 1 H, $J = 4.7$ Hz, $J = 8.3$ Hz), 3.12 (s, 3 H),

3.02 (s, 3 H): ^{13}C NMR (CDCl_3) δ 154.48, 148.03, 146.10, 143.48, 129.16, 123.52, 36.65, 36.35.

1-Methyl-3-(N,N-dimethylcarbamoyloxy)pyridinium Iodide (29b) A mixture of **29a** (9.8 g, 58.97 mmol) and methyl iodide (7.3 mL, 118 mmol) in dry THF (50 mL) was magnetically stirred overnight. The resulting precipitate was filtered and recrystallized with acetone/ether to give **29b** as a white solid (14.25 g, 78.4%): ^1H NMR (CDCl_3) δ 8.83 (s, 1 H), 8.68 (d, 1 H, $J = 6.0$ Hz), 8.37 (d, 1 H, $J = 8.7$ Hz), 8.03-8.08 (dd, 1 H, $J = 6.0$ Hz, $J = 8.7$ Hz), 4.76 (DO-H), 4.40 (s, 3 H), 3.13 (s, 3 H), 3.00 (s, 3 H).

1-Methyl-1,2,5,6-tetrahydro-3-(N,N-dimethylcarbamoyloxy)pyridine (29c) To an ice-cooled solution of **29b** (1.54 g, 5 mmol) in MeOH (25 mL) was added NaBH_4 (0.75 g, 20 mmol) in small portions. The mixture was stirred in an ice bath for 30 min, then at room temperature for 1 h. The volume of solvent was carefully reduced and H_2O (10 mL) was added. The solution was saturated with NaCl then extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL) and dried (MgSO_4). Removal of solvent gave a pale yellow liquid **29c** (0.86 g, 96.6%): ^1H NMR (CDCl_3) δ 5.44 (ca. 1 H), 3.02 (dd, 2 H, $J = 2.4$ Hz, $J = 3.9$ Hz), 2.95 (s, 3 H), 2.93 (s, 3 H), 2.54 (t, 2 H, $J = 5.9$ Hz), 2.38 (s, 3 H), 2.23-2.29 (br m, 2 H); ^{13}C NMR (CDCl_3) δ 145.84, 110.97, 55.13, 51.23, 45.21, 36.46, 36.30, 24.04.

1,1-Dimethyl-1,2,5,6-tetrahydro-3-(N,N-dimethylcarbamoyloxy)pyridinium Tosylate (29d) (PN-226, BM17825) A mixture of **29c** (0.85 g, 4.78 mmol) and methyl tosylate (1.78 g, 9.57 mmol) in ether (5 mL) was stirred at room temperature for 1 h. The precipitate was filtered and washed several times with ether to give **29d** (1.63 g, 93%), as white solid from CH_3CN /ether: mp 146-7 °C; IR (KBr) ν_{max} 3040, 3028, 1718, 1697 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.74 (d, 2 H, $J = 7.9$ Hz), 7.14 (d, 2 H, $J = 7.9$ Hz), 5.61 (t, 1 H, $J = 3.4$ Hz), 4.04 (br s, 2 H), 3.75 (t, 2 H, $J = 6.1$ Hz), 3.41 (s, 6 H), 2.92 (s, 3 H), 2.89 (s, 3 H), 2.50 (br m, 2 H), 2.33 (s, 3 H); ^{13}C NMR (CDCl_3) δ 153.66, 143.82, 139.50, 139.11, 128.56, 125.70, 110.77, 60.55, 57.91, 51.65, 36.49, 36.32, 21.18, 19.96. Anal. Calcd for $\text{C}_{17}\text{H}_{30}\text{O}_5\text{N}_2\text{S}$: C, 55.12; H, 7.07; N, 7.56. Found: C, 55.19; H, 7.10; N, 7.61.

3-(N-Methylcarbamoyloxy)pyridine (30a) 3-Hydroxypyridine (4.75 g, 50 mmol) was carbamoylated as described for **2c** with methyl isocyanate (6 mL, 0.1 mol) in the presence of a catalytic amount of $\text{Bu}_2\text{Sn}(\text{OAc})_2$ in dry THF (40 mL). Column chromatography of the crude product on silica gel (CHCl_3 -MeOH, 9:1) gave **30a** (5.47 g, 72%) as a colorless oil: $R_f = 0.42$ (CHCl_3 -MeOH, 9:1); ^1H NMR (CDCl_3) δ 8.41-8.45 (ca, 1 H), 7.51-7.55 (m, 1 H), 7.27-7.32 (m, 1 H), 6.13 (br s, 1 H), 2.83 (d, 3 H, $J = 4.8$ Hz); ^{13}C NMR (CDCl_3) δ 154.47, 147.70, 145.77, 143.13, 129.07, 123.57, 27.40.

1-Methyl-3-(N-methylcarbamoyloxy)pyridinium Iodide (30b) A mixture of **30a** (2.43 g, 16 mmol) and methyl iodide (2 mL, 32 mmol) in dry THF (30 mL) was stirred at room temperature for 16 h and then evaporated to dryness to give a yellow oil. Crystallization of the crude product gave **30b** (3.28 g, 66%) as a yellow solid from MeOH/ether: ^1H NMR (D_2O) δ 8.84 (s, 1 H), 8.67 (d, 1 H, $J = 6.2$ Hz), 8.37 (d, 1 H, $J = 8.6$ Hz), 8.01 (dd, 1 H, $J = 6.2, 8.6$ Hz), 4.40 (s, 3 H), 2.83 (s, 3 H).

1-Methyl-1,2,5,6-tetrahydro-3-(N-methylcarbamoyloxy)pyridine (30c) To an ice-cooled solution of **30b** (1.84 g, 6.25 mmol) in methanol (10 mL) was added NaBH_4 (0.97 g, 25 mmol) in small portions. The mixture was stirred at 0 °C for 30 min, then at room temperature for 1 h. The organic solvent was evaporated under vacuum and the white residue was dissolved in H_2O . The aqueous mixture was extracted with CH_2Cl_2 (6 x 30 mL). The combined organic layers were dried (MgSO_4) and evaporated to dryness to give a brown oil. Purification of the crude product by column chromatography on silica gel (CHCl_3 -MeOH, 9:1) gave **30c** (0.74 g, 70%) as white crystals from acetone/hexane: mp 86.5-87.5 °C; $R_f = 0.27$ (CDCl_3 -MeOH, 9:1); IR (KBr) $_{\text{vmax}}$ 1730 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.46 (br s, 1 H), 4.80 (br s, 1H), 3.01 (br s, 2 H), 2.82 (d, 3 H, $J = 4.8$ Hz), 2.53 (t, 2 H, $J = 5.7$ Hz), 2.38 (s, 3 H), 2.24 - 2.28 (m, 2 H). Anal. Calcd for $\text{C}_8\text{H}_{14}\text{N}_2\text{O}_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.36; H, 8.27; N, 16.39.

1,1-Dimethyl-1,2,5,6-tetrahydro-3-(N-methylcarbamoyloxy)pyridinium Iodide (30d) (PN-II-198, BN34821) Following the general procedure for Quaternization, the reaction of **30c** (0.45 g, 2.64 mmol) with methyl iodide (0.5 mL, 7.9 mmol) in dry

THF (4 mL) gave **30d** (0.75 g, 91%) as a white solid from CH₃CN/ether: mp 172-173 °C; IR (KBr)_{vmax} 1730, 1709 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.59 (br m, 1 H), 5.67 (br s, 1 H), 4.00 (br s, 2 H), 3.45 (t, 2 H, J = 6.2 Hz), 3.12 (s, 6 H), 2.59 (d, 3 H, J = 4.5 Hz), 2.46 - 2.54 (m, 2 H); ¹³C NMR (DMSO-d₆) δ 153.88, 138.76, 110.25, 59.49, 57.27, 50.79, 26.93, 19.23. Anal. Calcd for C₉H₁₇IN₂O₂: C, 34.63; H, 5.50; N, 8.97. Found: C, 34.72; H, 5.51; N, 9.02.

1-Methyl-4-(N,N-dimethylcarbamoyloxy)pyridinium Iodide (31b) (15) To an ice-cooled solution of 4-hydroxypyridine (4.75 g, 50 mmol) in dry DMF (70 mL) was added NaH (1.65 g, 55 mmol) in small portions. After being stirred at room temperature for 30 min, the mixture was cooled in an ice bath and N,N-dimethylcarbamoyl chloride (10.75 g, 0.1 mol) was added slowly via a syringe. The reaction mixture was then stirred at 80 °C for 5 h, cooled and quenched with H₂O (30 mL) followed by aqueous 10% HCl solution (50 mL), saturated with NaCl, then extracted with CH₂Cl₂ (3 x 30 mL). The aqueous phase was basified with 20% NaOH solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried (Na₂SO₄) and filtered through a short column of silica gel. Removal of the solvent gave **31a** as a yellow liquid (3.53g, 42%): ¹H NMR (CDCl₃) δ 8.57 (d, 2 H, J = 4.8 Hz), 7.13 (d, 2 H, J = 4.8 Hz), 3.10 (s, 3 H), 3.02 (s, 3 H).

A mixture of **31a** (0.86 g, 5.18 mmol) and methyl iodide (0.64 mL) in dry THF (10 mL) was stirred at room temperature overnight. The precipitate was filtered and recrystallized with methanol/ether to give **31b** (1.50 g, 94%): mp 149-150 °C (lit. 131- 132 °C).

1-Methyl-1,2,5,6-tetrahydro-4(N,N-dimethylcarbamoyloxy)pyridine (31c) Following the procedure described for **29c**, the reduction of **31b** (1.17 g, 3.8 mmol) with NaBH₄ (0.58 g, 15.2 mmol) in methanol (15 mL) gave **31c** as a liquid (0.65 g, 96%): ¹H NMR (CDCl₃) δ 5.32-5.37 (ca, 1 H), 3.02 (ddd, 2 H, J = 2.7 Hz, J = 3.5 Hz, J = 9.2 Hz), 2.93 (br s, 6 H), 2.65 (dd, 2 H, J = 5.7 Hz, J = 12.3 Hz), 2.30-2.40 (overlapped, 5 H); ¹³C NMR (CDCl₃) δ 154.53, 146.85, 111.04, 52.77, 51.75, 45.02, 36.29, 36.20, 27.74.

1,1-Dimethyl-1,2,5,6-tetrahydro-4(N,N-dimethylcarbamoyloxy)pyridinium

Tosylate (32) (PN-236, BM17834) To a solution of **31c** (0.63 g, 3.53 mmol) in dry CH₃CN (20 mL) was added methyl tosylate (1.316 g, 7.00 mmol). After being stirred at room temperature for 2 h, the reaction mixture was warmed on a steam bath and ether was added. The reaction mixture was then cooled on an ice bath to give a white solid **32** (1.07 g, 83%): mp 159-9.5 °C from CH₃CN/ether; IR (KBr) ν_{max} 3032, 3022, 1718, 1190 cm⁻¹; ¹H NMR (CDCl₃) δ 7.72 (d, 2 H, J = 7.9 Hz), 7.14 (d, 2 H, J = 7.9 Hz), 5.33 (br s, 1 H), 4.16 (br d, 2 H, J = 3.0 Hz), 3.78 (t, 2 H, J = 6.5 Hz), 3.41 (s, 6 H), 2.95 (s, 3 H), 2.92 (s, 3 H), 2.56 (br m, 2 H), 2.33 (s, 3 H); ¹³C NMR (CDCl₃) δ 153.6, 145.4, 143.8, 139.2, 128.7, 125.7, 106.5, 60.0, 58.7, 51.2, 36.5, 36.3, 23.8, 21.2. Anal. Calcd for C₁₇H₃₀O₅N₂S: C, 55.12; H, 7.07; N, 7.56. Found: C, 55.12; H, 7.12; N, 7.53.

2-(4 -Hydroxyphenyl)imidazo[1,2-a]pyridine A general procedure (16) was followed in the synthesis of 2-(4 -hydroxyphenyl)-imidazo[1,2-a]pyridine hydrobromide from 2-aminopyridine and α -bromo-4-hydroxyacetophenone. The resulting salt was suspended in water and excess sodium bicarbonate was added. The mixture was stirred vigorously for 12 h. The product was obtained after filtration and washed with water.

1-Methyl-2-(4 -hydroxyphenyl)imidazo[1,2-a]pyridinium Chloride (KC012, BM14306) A general procedure for Quaternization was followed, which included methylation with iodomethane and anion exchange with Amberlite resin. Recrystallization from hot acetonitrile gave 72% yield of the desired product: mp 233-235 °C; IR (KBr) ν_{max} 3397, 3073, 3051, 1614, 1504, 1282 cm⁻¹; ¹H NMR (D₂O) δ 8.58 (d, 1 H), 7.99 (s, 1 H), 7.89 (m, 2 H), 7.43 (m, 3 H), 6.93 (d, 2 H). Anal. Calcd for C₁₄H₁₃ClN₂O. 0.25 H₂O: C, 63.39; H, 5.13; N, 10.57; Cl, 13.37. Found: C, 62.98; H, 5.12; N, 10.61; Cl, 13.34.

References:

- (1) R. J. Sundberg, D. Dalvie, J. Cordero, M. Sabat and H. A. Musallam, *Chem. Res. Toxicol.* **6**, 500 (1993); R. J. Sundberg, D. Dalvie, J. Cordero and H. A. Musallam, *Chem. Res. Toxicol.* **6**, 506 (1993).
- (2) M. K. Gilson, T. P. Straatsma, J. A. McCommon, D. R. Ripoll, C. H. Faerman, P. H. Axelson, I. Silman and J. L. Sussman, *Science*, **265**, 1276 (1994); I. Silman, M. Harel, J. Eichler, J. L. Sussman, A. Anselmet and J. Massoulie, Alzheimer Disease: Therapeutic Strategies, E. Giacobini and R. Becker editors, Birkhauser Biston, 1994.
- (3) I. Schalk, L. Ehret-Sabatier, F. Bouet, M. Goeldner and C. Hirth, *Eur. J. Biochem*, **219**, 155 (1994).
- (4) S. Ohta, T. Yamamoto, I. Kawasaki, M. Yamashita, H. Katsuma, R. Nasako, K. Kobayashi and K. Ogawa, *Chem. Pharm. Bull.* **40**, 2681 (1992).
- (5) O. A. Seide and A. I. Titow, *Chem. Ber.*, **69**, 1884 (1936), *CA*, **30**: 7739³ (1936).
- (6) M. Gaudry and A. Marquet, *Org. Synth*, **55**, 24 (1976).
- (7) J. A. Moore, and F. Marascia, *J. Am. Chem. Soc.* **81**, 6049 (1959), for details of the procedure see: Final Report, DAMD 17-89-C-9014, June, 1991, P45.
- (8) R. Graf, *Chem. Ber.*, **64**, 21 (1931); G. B. Barlin and W. Pfeleider, *J. Chem. Soc. B*, 1425 (1971); L. W. Deadly, O. L. Korytsky and J. E. Rowe, *Aust. J. Chem.*, **35**, 2025 (1982); R. J. Sundberg and S. Jiang, manuscript in preparation.
- (9) R. Rydzkowski, D. Blondeaw and H. Sliwa, *Tetrahedron Lett*, **26**, 2571 (1985); R. Rydzkowski, D. Blondeaw, H. Sliwa and C. Caze, *J. Chem Res. (Symp)* **50**, (1986); J. Kaminski, et al, *J. Med. Chem.* **28**, 876 (1985).

- (10) B. H. Lee, T. C. Stelly, W. J. Colucci, J. G. Gaicie, R. D. Gandour and D. M. Quinn, *Chem. Res. Toxicol.*, **5**, 411 (1992).
- (11) G. L. Ellman, K. D. Courtrey, V. Andres, Jr. and R. M. Featherstone, *Biochem. Pharmacol.*, **7**, 88 (1961).
- (12) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 383 (1949); R. Grindley and F. L. Pyman, *J. Chem Soc.*, 3128 (1927).
- (13) Prepared from 2-(lithiomethyl)-1-methyl-*1H*-imidazole and predried formaldehyde, cf. D. S. Noyce, G. T. Stowe and W. Wong, *J. Org. Chem.*, **39**, 2301 (1974).
- (14) Prepared from 2-(lithiomethyl)-1-methyl-*1H*-imidazole and ethylene oxide.
- (15) Zhao, Z.; Dalvie, D.; Naiman, N.; Castagnoli, K.; Castagnoli Jr., N. *J. Med. Chem.*, **35**, 4473 (1992).
- (16) R. J. Sundberg, D. J. Dahlhausen, G. Manikuman, B. Marunkel, A. Biswas, V. Srinivasan, F. King, Jr. and P. Waid, *J. Heterocycl. Chem.*, **25**, 129 (1988).



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y)

21 Apr 97


MEMORANDUM FOR Administrator, Defense Technical Information
Center, ATTN: DTIC-OCF, Fort Belvoir,
VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for Contract Number DAMD17-92-C-2081. Request the limited distribution statement for Accession Document Numbers ADB188021, ADB200784, ADB175882, and ADB211649 be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322.

FOR THE COMMANDER:


GARY R. GILBERT
Colonel, MS
Deputy Chief of Staff for
Information Management

*Completed
1-10-00
B.W*